EU Risk Management Plan
for
Zepzelca (lurbinectedin)

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List of Abbreviations

ABP	Arterial Blood Pressure
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BRCA	BReast CAncer gene
CAV	Cyclophosphamide, Doxorubicin and Vincristine
CDX	Cell-Derived Xenograft
CE	Carboplatin/Etoposide
CG	Cytosine-Guanine
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum Concentration
CNS	Central Nervous System

CPK	Creatine Phosphokinase
CrCl	Creatinine Clearance
CT	Computed Tomography
CYP	Cytochrome P450
CYP1A2	Cytochrome P450 1A2
CYP3A4	Cytochrome P450 3A4
D	Day
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ES-SCLC	Extensive-Stage Small Cell Lung Cancer
EU	European Union
FD	Flat Dose
FDA	Food and Drug Administration
G-CSF	Granulocyte Colony-Stimulating Factor
GGT	Gamma-Glutamyl Transferase
hERG	Human Ether-à-go-go-Related Gene
HI	Hepatic Impairment
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
i.v.	Intravenous
IC	Inhibitory Concentration
IIS	Investigator Initiated Studies
INN	International Non-proprietary Name
ISA	Integrated Safety Analysis
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MDR1	Multidrug Resistance protein 1 or P-gp
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP	Non-Human Primates
NSCLC	Non-Small Cell Lung Cancer
OATP1B1	Organic-Anion-Transporting Polypeptide 1B1
OATP1B3	Organic-Anion-Transporting Polypeptide 1B3
OCT1	Organic Cation Transporter 1
ORR	Objective Response Rate
OS	Overall Survival
PBPK	Physiologically Based Pharmacokinetic
PBRER	Periodic Benefit Risk Evaluation Report
PD-L	Programmed Death-Ligand
PDX	Patient-Derived Xenograft
PFS	Progression-Free Survival
P-gp	P-glycoprotein or MDR1
PK	Pharmacokinetic

PK/PD	Pharmacokinetic/Pharmacodynamic
PLD	Pegylated Liposomal Doxorubicin
PR	PR interval (from the beginning of the P wave until the beginning of the QRS complex on ECG)
PSUR	Periodic Safety Updated Report
PT	Preferred Term (of MedDRA)
q3wk	Every 3 weeks
QPPV	Qualified Person for Pharmacovigilance
QRS	QRS complex
QT	QT interval (from the start of the Q wave to the end of the T wave on ECG)
QTcF	QT interval corrected using Fridericia's formula
QTcV	QT interval corrected according to the Van de Water formula.
RD	Recommended Dose
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAKK	Swiss Group for Clinical Cancer Research
SCLC	Small Cell Lung Cancer
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class (of MedDRA)
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
US	United States

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	Lurbinectedin
Pharmacotherapeutic group(s) (ATC Code)	ATC Code: L01XX69 L01XX Other antineoplastic agents
Marketing Authorisation Holder or Applicant	Pharma Mar, S.A. Avda. de los Reyes 1, Pol. Ind. La Mina 28770 Colmenar Viejo (Madrid), Spain
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Zepzelca
Marketing authorisation procedure	Centralised Procedure

Brief description of the product	Chemical class: Lurbinectedin (PM01183, PM1183, tryptamicidin) is a new synthetic compound, structurally related to ecteinascidins that contains a mono-bridged pentacyclic skeleton composed of two fused tetrahydroisoquinoline rings linked to a 10-membered lactone bridge through a benzylic sulphide linkage with an additional tetrahydro-β-carboline ring attached to the rest of the structure through a spiro ring. Chemical name: (1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-8,14-dihydroxy-6',9-dimethoxy-4,10,23-trimethyl-19-oxo-2',3',4',6,7,9',12,13,14,16-decahydro-6a*H*-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: 784.87g/mol.
	Summary of mechanism of action: Lurbinectedin is an inhibitor of oncogenic transcription that covalently binds to cytosine guanine (GC)-rich promoter regions of protein-coding genes. This disrupts the binding of oncogenic transcription factors to their recognition sequences. Additionally, lurbinectedin forms deoxyribonucleic acid (DNA) adducts that trigger the ubiquitin-proteasome-mediated degradation of elongating ribonucleic acid (RNA) polymerase II, further suppressing transcription. These DNA adducts are typically repaired by the nucleotide excision repair system; however, this process can generate secondary double-strand DNA breaks. Consequently, cell cycle progression is delayed in the S and G2/M phases, leading to caspase-dependent cell death. Beyond its direct cytotoxic effects, lurbinectedin modulates the tumour microenvironment, particularly affecting tumour-associated macrophages and inflammatory signalling pathways. Lurbinectedin treatment also activates the STING pathway, leading to increased interferon signalling, upregulation of pro-inflammatory chemokines, and enhanced expression of major histocompatibility complex class I (MHC-I), thereby contributing to an immunogenic tumour response.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	
Indication(s) in the EEA	Current: Zepzelca, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: The recommended dose of lurbinectedin is 3.2 mg/m^2 every 21 days until disease progression or unacceptable toxicity as a combination therapy with atezolizumab. When administering lurbinectedin on the same day, atezolizumab should be administered first. For the recommended intravenous (i.v.) or subcutaneous dose of atezolizumab, as well as for recommendations regarding dose modification due to toxicity, refer to their prescribing information.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): Powder for concentrate for solution for infusion; Zepzelca 2 mg and 4 mg as lyophilized white to off-white powder for concentrate for solution for infusion.
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication:

Lurbinectedin, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.

The recommended dose of lurbinectedin is 3.2 mg/m^2 by intravenous (i.v.) infusion over 60 minutes every 21 days until disease progression or unacceptable toxicity as a combination therapy with atezolizumab.

Lurbinectedin is also indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) who have progressed on or after prior platinum-containing therapy in some countries outside the European Union (EU), including Switzerland, Canada and the United States of America among others.

Incidence:

Approximately 250,000 patients are diagnosed with SCLC each year globally, of which approximately 200,000 succumb to the disease (1). In Europe, the incidence of all lung cancer is 484,554: Central and Eastern Europe 158,147; Western Europe 145,878; Southern Europe 107,139 and Northern Europe 73,390 (2).

By nature, and by predisposition, this highly aggressive neuroendocrine tumour doubles rapidly and disseminates widely early on, so that 80-85% of patients are diagnosed with advanced or ES-SCLC (3).

Prevalence:

Lung cancer is the most common cancer in males with an estimated 1.4 million cases globally and the third most common cancer in females with 0.77 million cases in 2020. It continues to be the leading cancer-related death for males and second for females. The SCLC accounts for approximately 14% of all lung cancer cases (1). GLOBOCAN shows that the estimated prevalence at 5 years of lung cancer is 378,694 in the EU-27+3 (2).

Demographics of the population in the proposed indication and risk factors for the disease:

Lung cancer mainly occurs in patients over 65 years old and the average age at diagnosis is approximately 70 years. It rarely occurs in patients who are younger than 45 years (4).

The incidence of SCLC is higher among people with low socioeconomic status, which parallels the patterns of tobacco consumption. Though the 2-year relative survival for limited-stage SCLC has improved from 36% in 2001 to 2002 to 46% in 2015 to 2016, prognosis remains poor for patients with extensive disease, with 2-year relative survival at 7% to 8% and a median survival of 7 months (1).

Approximately 10-25% of patients with extensive-stage disease are diagnosed with brain metastases at initial presentation, and an additional 40-50% will develop them during their disease. Limited stage SCLC, which has not metastasized, is potentially curable, whereas ES-SCLC is not (3).

The main risk factor for SCLC is cigarette smoking, particularly with early age of starting and duration of smoking. Approximately 2%–3% of SCLC cases in never-smokers have been attributed to environmental and occupational exposures, including radon. SCLC in never-smokers may also occur in patients who have histologic transformation from adenocarcinoma, particularly in those harbouring epidermal growth factor receptor (EGFR) mutation and acquired resistance to EGFR tyrosine kinase inhibitors (5).

The main existing treatment options:

Main existing treatment options in first line:

Patients with limited-stage SCLC can be treated with chemotherapy and radiation with the potential for long-term survival (6) though the majority will relapse. The majority of patients with SCLC are initially diagnosed with ES-SCLC, which has poor survival prospects: median overall survival (OS) of approximately 10-12 months (7),(8).

The current standard first-line treatment for patients with ES-SCLC is atezolizumab plus carboplatin/etoposide (CE), as induction therapy, followed by atezolizumab maintenance therapy, or durvalumab plus platinum (cisplatin or carboplatin) and etoposide as induction therapy, followed by durvalumab maintenance therapy (9), (10).

Atezolizumab combined with CE for the first-line treatment of patients with ES-SCLC was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2019 based on the results of the GO30081 (IMpower133) study. In the randomised phase III Study IMpower133, a total of 201 patients were randomly assigned to the atezolizumab plus CE group, and 202 patients to the placebo plus CE group. At a median follow-up of 13.9 months, the hazard ratio (HR) for death was 0.70 (95% CI, 0.54-0.91; p=0.007) with a median OS of 12.3 months in the atezolizumab plus CE group and 10.3 months in the placebo plus CE group. The HR for progression-free survival (PFS) was 0.77 (95% CI, 0.62-0.96; p=0.02) with a median PFS of 5.2 months and 4.3 months, for atezolizumab plus CE and placebo plus CE, respectively. The safety profile of atezolizumab plus CE was consistent with the previously reported safety profile of the individual agents, with no new findings observed (8).

Durvalumab was approved in 2020 by the FDA and the EMA for the first-line treatment of adults with ES-SCLC in combination with a choice of chemotherapies, etoposide plus either carboplatin or cisplatin based on the results of the CASPIAN trial that met the primary endpoint of OS for durvalumab plus chemotherapy, reducing the risk of death by 27% versus chemotherapy alone (based on a HR of 0.73; 95% confidence interval (CI) 0.59-0.91; p=0.0047), with median OS of 13.0 months versus 10.3 months for chemotherapy alone (11).

Recently, on 05 February 2025, serplulimab in combination with CE was approved in Europe for the first-line treatment of patients with ES-SCLC based on data from the phase III ASTRUM-005 trial (NCT04063163) (12). In this double-blind phase III randomised clinical trial, patients were randomized 2:1 to receive either 4.5 mg/kg of serplulimab (n = 389) or placebo (n = 196) intravenously every 3 weeks. All patients received i.v. carboplatin and etoposide every 3 weeks for up to 12 weeks. At time of the OS interim analysis (with a median follow-up of 12.3 months), the median OS was 15.4 months (95%CI, 13.3 months-not evaluable) for serplulimab versus 10.9 months (95%CI, 10.0-14.3 months) for placebo (HR, 0.63; 95%CI, 0.49-0.82). The median PFS (assessed by an independent radiology review committee) was 5.7 months (95% CI, 5.5-6.9 months) for serplulimab versus 4.3 months (95% CI, 4.2-4.5 months) for placebo (HR, 0.48; 95% CI, 0.38-0.59).

More recently, on 01 April 2025, the EMA has issued a positive opinion recommending the approval of tislelizumab in combination with etoposide and platinum chemotherapy for the first-line treatment of adult patients with ES-SCLC. The recommendation was supported by data from the phase III RATIONALE-312 trial, which showed that at a median follow-up of 14.2 months, patients treated with the combination of tislelizumab and chemotherapy (n=227) achieved a median OS of 15.5 months (95% CI, 13.5-17.1) compared with 13.5 months (95% CI, 12.1-14.9) for those given placebo plus chemotherapy (n=230; HR=0.75; 95% CI, 0.61-0.93; p=0.0040). Tislelizumab plus chemotherapy generated a median PFS of 4.7 months (95% CI, 4.3-5.5) compared with 4.3 months (95% CI, 4.2-4.4) for placebo plus chemotherapy (HR=0.64; 95% CI, 0.52-0.78; p < 0.0001 (13).

Despite the improved efficacy observed with first-line programmed death-ligand 1 (PD-L1) inhibitors plus platinum (cisplatin or carboplatin) and etoposide, most patients with ES-SCLC experience disease

progression and upon relapse, their prognosis is poor. Therefore, novel strategies are needed to achieve better long-term outcomes.

The early introduction of agents active in SCLC, and with a complementing pathway to the current first-line treatment approach, is an appealing strategy to further improve the prognosis of patients with advanced SCLC.

Main existing treatment options in second line:

Following relapse, patients are categorized as "sensitive" and "resistant" according to duration of response to initial chemotherapy. Relapse > 90 days after the last exposure to first-line chemotherapy is termed "sensitive" provided there is no progression or a complete or partial response was achieved, whereas failure to respond to the first-line chemotherapy or recurrence < 90 days after the last exposure to first-line chemotherapy is termed "resistant". Second-line options include rechallenge with a first-line platinum regimen, which is usually reserved for chemosensitive disease, topotecan or lurbinectedin (3).

a) *Topotecan*

Topotecan, a topoisomerase 1 inhibitor, was approved in 1998 based on a randomized phase III trial clinical trial with 211 patients that relapsed at least 60 days after their initial treatment. Patients received either an i.v. infusion of topotecan (1.5 mg/m²) as a single agent for 5 consecutive days every 3 weeks or CAV (cyclophosphamide, 1,000 mg/m², adriamycin, 45 mg/m², and vincristine, 2 mg) administered intravenously on day 1 every 3 weeks. While median survival, time to progression and overall response rate were comparable between the two groups, toxicity was not: shortness of breath (p = 0.002), fatigue (p = 0.032), hoarseness (p = 0.043), and anorexia (p = 0.042) were significantly improved in favour of topotecan as was interference with daily activities (p = 0.023). A randomized phase III trial to compare oral topotecan with i.v. topotecan in relapsed SCLC, in which, out of 309 patients, 153 patients received oral topotecan 2.3 mg/m^2 daily for five consecutive days every three weeks and 151 received i.v. topotecan 1.5 mg/m^2 daily for five consecutive days every three weeks, showed a similar objective response rate (ORR) in both arms of 18.3% *vs.* 21.9% respectively, and no difference in median time to response (6.1 weeks for both), median duration of response (18.3 weeks *vs.* 25.4 weeks), and median time to progression (11.9 weeks *vs.* 14.6 weeks). Nevertheless, topotecan is associated with dose-limiting hematologic toxicities such as neutropenia, anaemia and thrombocytopenia, non-hematologic toxicities such as fatigue, alopecia, nausea, and diarrhoea, a response rate <20% and a treatment scheme of five consecutive days which limits its use in practice. Also, topotecan is approved only for those patients with platinum sensitivity (3).

b) *Carboplatin plus etoposide rechallenge*

In an open-label, 1:1 randomized, phase III French trial from 2020 with PFS as the primary endpoint, 164 patients with histologically or cytologically confirmed advanced stage IV or locally relapsed SCLC, who responded to first-line platinum plus etoposide treatment but relapsed or progressed ⩾90 days after completion of first-line treatment were enrolled. The results demonstrated a median PFS that was significantly longer in the platinum doublet group than in the topotecan group (4.7 months vs 2.7 months, hazard ratio 0.57; p=0.0041), suggesting that CE is the preferred option in patients with sensitive relapsed SCLC. Median OS was not significantly longer in the combination chemotherapy group compared with the topotecan group (3).

In an open-label, 1:1 randomized, phase III, Japanese trial from 2016 with 180 patients enrolled and with OS as the primary endpoint, cisplatin + etoposide + irinotecan was compared with topotecan. Overall survival was significantly longer in the combination chemotherapy group (median 18.2 months

vs. 12.5 months), leading to the authors to suggest replacement of topotecan as second line standard of care with the combination of cisplatin + etoposide + irinotecan (3).

c) *Lurbinectedin*

A synthetic derivative of the marine drug trabectedin, lurbinectedin is a DNA binding agent that selectively inhibits RNA polymerase II transcription, and which has demonstrated activity against SCLC both as a single agent and in combination with doxorubicin. Based on a single arm, multicenter, phase II basket trial in a mixed population of platinum-sensitive and platinum-resistant patients treated with 3.2 mg/m^2 of i.v. lurbinectedin every 3 weeks, which demonstrated an ORR of 35.2% (95%CI: 26.2-45.2), an overall median duration of response of 5.3 months (95%CI: 4.1-6.4), a median PFS of 3.5 months (95%CI: 2.6-4.3) and a median OS of 9.3 months (95%CI: 6.3-11.8), lurbinectedin received accelerated FDA approval on June 15, 2020 in second line after progression on platinum-based chemotherapy. Hematologic toxicities included grade 4 neutropenia in 25% of the patients, grade 4 thrombocytopenia in 4% and 10% of the patients experienced serious adverse events, of which neutropenia and febrile neutropenia were the most common. Non-hematologic toxicities included fatigue, decreased appetite, and gastrointestinal symptoms (3).

Natural history of the indicated condition in the <untreated> population, including mortality and morbidity:

Prognosis remains poor for patients with extensive disease, with 2-year relative survival at 7% to 8% and a median survival of 7 months. Unlike in non-SCLC (NSCLC), there had been no major treatment advancement in the past few decades in addition to the standard combination of platinum-based chemotherapy and radiation until 2018. Several phase III clinical trials have evaluated the efficacy of additional immunotherapy including atezolizumab and durvalumab (recommended by the European Society for Medical Oncology and National Comprehensive Cancer Network) and serplulimab and tislelizumab in patients with ES-SCLC, with the median overall survival improvement ranging from 2 to 4.5 months compared with chemotherapy alone. Nevertheless, the degree of benefit from immunotherapy was less compared with NSCLC (1).

Important co-morbidities:

Major co-morbidities are highly prevalent in patients with lung cancer due to its strong association with smoking and aging. Chronic obstructive pulmonary disease (25–50%) and cardiovascular disease (approximately 25%) are the most common comorbid conditions among these patients (14).

In a population-based cohort study from French cancer registries, the presence of comorbidity based on Charlson Comorbidity Index grades 1–2 and ⩾3 was associated with lower survival rates for SCLC after adjustment for age, sex, stage and diagnostic mode (15).

All patients (n=4,142) diagnosed with SCLC from 1995 to 2012 from the population-based Netherlands Cancer Registry in the Eindhoven region were evaluated for trends in the prevalence of comorbidity and its prognostic impact. The prevalence of comorbidity increased from 55% in 1995 to 1998 to 76% in 2011 to 2012 and multimorbidity (i.e., ⩾2 concomitant diseases) from 23% to 51%. The prevalence of comorbidity increased with age. Among men, hypertension, cardiac disease, and diabetes became more common (increased from 11% to 35%, from 19% to 36%, and from 7% to 18%, respectively). In women, the rate of pulmonary disease, hypertension, and cardiac disease increased the most (increased from 18% to 30%, from 12% to 28%, and from 11% to 24%, respectively). Multi-morbidity was associated with a slightly increased hazard of death in those with limited-stage SCLC, independent of treatment. However, the prognostic effects in those with advanced-stage SCLC resulted from treatment. Digestive disease favourably affected survival and cardiac disease negatively affected the prognosis for

those with limited-stage SCLC, and cardiac and cerebrovascular diseases had a negative prognostic effect for those with ES-SCLC (16).

Part II: Module SII - Non-clinical part of the safety specification

Lurbinectedin binds to DNA preferentially to guanines located within the promoter area of protein coding genes, acting as an inhibitor of oncogenic transcription. *In vitro*, lurbinectedin demonstrated antiproliferative effects against a broad selection of tumour types, including representative cell lines of lung, kidney and prostate tumors, as well as leukemia, with IC_{50} values in the range of 1-10 nM. Lurbinectedin exhibits antitumor activity against different experimental models of either subcutaneously or orthotopically xenografted human-derived (CDX and PDX) tumors such as lung, breast, prostate, bladder, kidney, ovary, pancreas and sarcoma.

Based on *in vitro* assays, off-target pharmacological effects induced by lurbinectedin are considered unlikely.

The potential effects of lurbinectedin on major organ systems were assessed *in vitro* (cardiovascular) and *in vivo* (central nervous system [CNS], respiratory and cardiovascular). *In vivo* studies were conducted by single i.v. bolus administration of lurbinectedin around maximum tolerated dose (MTD) to rats, non-human primates (NHP) and dogs.

Lurbinectedin has been tested in rats, dogs, and NHP via the i.v. route either as single or multi-cycle of bolus i.v. every 3 weeks up to 8 cycles. Lurbinectedin has demonstrated strong *in vitro* activity in several human cancer cell lines, representative of prostate, pancreas, ovary, NSCLC and SCLC, liver, leukaemia, lymphoma, kidney, gastric, colon and breast tumour cell lines.

The primary toxicity identified in non-clinical species (rat, dog and NHP) was characterized by severe, reversible and non-cumulative atrophy of bone marrow, which was associated with dose-related leukopenia, as well as thrombocytopenia and anaemia.

Key safety findings from non-clinical studies and relevance to human usage:

(from non-clinical studies)	**Relevance to human usage**
Single dose toxicity	
Rats The MTD after single i.v. bolus dose was 0.2 and 0.1 mg/kg (1.2 and 0.6 mg/m^2) in male and female rats respectively. Dogs The MTD after single i.v. bolus dose was 0.03 mg/kg (0.6 mg/m^2). NHP The MTD after single i.v. bolus dose was 0.125 mg/kg (1.5 mg/m^2). Largely reversible adverse effects were noted in the reticuloendothelial system, bone marrow, gastrointestinal tract and at the injection site. At MTD and above, liver (mainly in rats) and kidneys were also identified as target toxicity organs.	The discussions of relevance to human usage are provided under specific topic headings.
Repeat dose toxicity	
Rats After repeated dosing (4 and 8 cycles) the MTD was estimated as 0.06 mg/kg (0.36 mg/m^2) for males and 0.03 mg/kg (0.18 mg/m^2) for females. At MTD, moderate leukopenia as well as severe reticulocytopenia was observed, with both returning to normal values 3 weeks	Target organs of lurbinectedin's toxicity were identified. The findings described in animals correlate with the most commonly reported lurbinectedin-induced adverse events (AEs) in patients. Further discussions on the relevance to human usage are provided under specific topic headings.

(from non-clinical studies)	Relevance to human usage
after the last dose, in agreement with a strong, but transient reduction in the erythroid series in the bone marrow. Clinical chemistry results indicated dose-related, slight and transient increases in bilirubin as well as marginal increases in blood urea nitrogen and decreases in triglycerides. Microscopy examinations revealed changes in the hematopoietic system: bone marrow (mild decreased cellularity with prominent adipose and vascular tissues); spleen (minimal-to-mild loss of lymphocytes and/or decreased red pulp); thymus (decrease in lymphocytes and thinner, irregular cortex with lack of cortico-medullar demarcation); injection site (mild-to-severe necrosis); and stomach (hyperplasia of mucosal squamous epithelium in the forestomach). Above the MTD, in the 4-cycle study, additional findings were recorded: body weight decreased, hepatic and cholestasis markers markedly increased, concomitantly with alteration in coagulation factors, ionic and protein values and hepatocellular necrosis associated with subacute inflammatory reaction and haemorrhage in the liver. <u>Dogs</u> Following 4 cycles of administration, the MTD of lurbinectedin was estimated to be 0.03 mg/kg (0.6 mg/m^2). At MTD, treatment-related clinical signs were limited to sporadic, minor and transient reductions in body weight, food and water consumption, as well as liquid faeces and emesis. Haematological evaluation revealed a moderate leukopenia as well as severe, dose-related reticulocytopenia that returned to normal values by the end of the recovery period, in agreement with a moderate depletion of bone marrow cells and severe damage of the few cells still present, as well as a strong reduction in the erythroid series. Clinical chemistry evaluation showed minor fluctuations, (although significant) of some parameters, such as creatinine kinase, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), glucose and chloride. Histopathological evaluation showed haemorrhage and/or oedema and/or necrosis, associated in some instances with inflammatory reactions at the injection site, mainly in animals receiving the MTD. <u>NHP</u> After repeated dosing once every 3 weeks for 4 and 8 cycles, the MTD of lurbinectedin was 0.125 mg/kg (1.5 mg/m^2) in both genders. The main clinical signs associated with lurbinectedin treatment were emesis and liquid faeces, as well as dose unrelated, short-lasting decreased appetite and/or food intake, observed after each cycle in the majority of treated animals without a clear impact on body weight reduction. Haematology evaluations revealed a dose-dependent, non-cumulative leukopenia, mainly reticulocytopenia. Above the MTD, anaemia and thrombocytopenia were noted. In the clinical chemistry evaluations performed 7	

(from non-clinical studies)	Relevance to human usage
days after each lurbinectedin administration, the only noticeable findings were minimal increases in ALT and aspartate aminotransferase (AST). At histopathology, dose-dependent bone marrow hypocellularity and lymphoid depletion in the thymus and spleen were detected. After 4 cycles of treatment, microscopy examinations further revealed villous atrophy in the duodenum, ileum and jejunum, as well as mucosal atrophy in the caecum. In the liver, inflammatory cell foci were seen, as well as reduced cellularity. On Day 85 (terminal sacrifice), lurbinectedin-related findings were focused on the gastro-intestinal tract and identified as villous atrophy in the ileum, jejunum and duodenum with inflammatory cell foci.	
Clinical signs and body weight	
Transient decrease in body weight and food consumption was seen in rats, NHP and dogs, likely related to hematopoietic and/or gastro-intestinal toxicity. Nausea and/or vomiting was regularly recorded (lasting 2-4 days post-dose) in NHP and dogs, regardless of the dose level and number of cycles.	In the integrated safety analysis (ISA) (n=554), the most common treatment-related (or with unknown relationship) AEs (all grades) were fatigue (52.5%), nausea (50.9%), vomiting (25.1%), decreased appetite (17.1%), constipation (16.8%), and diarrhoea (12.8%). The most common of these AEs to reach grade ≥3 were fatigue (7% of patients), febrile neutropenia (6.3%), nausea (3.1%), and vomiting (2.7%). The most common (all grades) treatment-related AEs for the SCLC cohort in PM1183-B-005-14 (n=105) were fatigue (59%), nausea (33.3%), decreased appetite (21.9%), vomiting (18.1%), and diarrhoea (13.3%). The only treatment-related (or with unknown relationship) AEs to reach grade ≥3 were fatigue (7.6%), febrile neutropenia (4.8%), pneumonia (1.9%), diarrhoea (1.0 %), and skin ulcer (1.0%).
Haematopoietic System	
In rats, NHP and dogs, dose-related leukopenia, lymphopenia and reticulocytopenia were observed, with no evidence of cumulative severity. Bone marrow atrophy, thymus atrophy and lymphoid depletion in the spleen were observed in all species. These alterations partially or completely recovered at the end of each 3-week cycle. Above the MTD, slight anaemia and thrombocytopenia were also reported.	In the ISA (n=554), the most common haematological abnormality (all grades, regardless of relationship) was anaemia (all grades, 92.1%; grade ≥3, 17.5%), with non-cumulative neutropenia as the most common grade ≥3 haematological abnormality occurring in 40.8% of patients. Grade ≥3 thrombocytopenia was reported in 9.7% of lurbinectedin-treated patients. In the SCLC cohort (n=105) of PM1183-B-005-14, the most common haematological abnormality (regardless of relationship) during treatment was anaemia (all grades, 94.3%; grade ≥3, 10.5%), with neutropenia as the most common grade ≥3 haematological abnormality occurring in 46.7% of patients. Grade ≥3 thrombocytopenia was reported in 6.7% of lurbinectedin-treated patients.
Clinical chemistry	
In NHP and dogs, at doses up to the MTD, biochemical changes were limited to slight, sometimes sporadic increases in liver function tests without association with histopathological changes. In rats (at MTD) and in other species (above the MTD), biochemical alterations were more pronounced: including increases in liver function, cholestasis markers, creatinine and blood urea nitrogen,	Reversible and non-cumulative grade 3/4 transaminase increases were the most common severe biochemical abnormalities in patients treated with lurbinectedin. Consistency was observed between the ISA and the PM1183-B-005-14 SCLC populations with respect to biochemical abnormalities (regardless of relationship). Transaminase increases were the most common grade 3/4 biochemical abnormalities; they occurred at similar

(from non-clinical studies)	Relevance to human usage
with decreases in cholesterol, albumin, and ionic perturbations.	frequencies (ALT 6.4% [grade 4 in 0.4%] and AST 3.3% [grade 4 in 0.5%] in the ISA population vs. ALT 3.9% and AST 1.9% [all grade 3] in the PM1183-B-005-14 SCLC population) and were reversible, asymptomatic and not cumulative over time.
Cardiac muscle	
Minimal to mild myocardial degeneration and/or necrosis were reported in several non-clinical toxicity studies with lurbinectedin. These findings were apparently more frequent following single dose administration in the rat and NHP, although they were also reported in the repeat-dose studies performed in NHP and dogs. Similar spontaneous, microscopically identified cardiomyopathy has been described in NHP, rats and dogs. In these studies, animals were clinically healthy and importantly, no remarkable changes were seen in the electrocardiogram (ECG) performed in NHP. In lurbinectedin-treated animals at dose levels lower than or equal to MTD, the relationship with lurbinectedin is unclear. However, a trend to increased frequency and severity at supra-MTD levels (particularly in rats) was suggested and, a relationship with lurbinectedin-related toxicity (e.g., severe bone marrow depression and poor general condition) preceding the death of the animals cannot be discounted.	In patients, no relevant clinical signs associated with cardiomyopathy were recorded. Lurbinectedin at the recommended dose and schedule (3.2 mg/m² every three weeks [q3wk]) did not induce clinically relevant QTcF prolongation or change in cardiac function.
Gastrointestinal tract	
In rats, NHP and dogs, reduction of the crypt size and/or number (up to atrophy) of the mucosa in the villous area, with possible inflammation associated with necrosis and/or haemorrhage in both small and large intestine were observed. More specifically in rats, hyperplasia of squamous epithelium with hyperkeratosis, occasionally with inflammatory reaction and/or mucosal ulceration and/or submucosal oedema was seen in the non-glandular region of the stomach (forestomach). These findings correlate with the emesis and soft faeces, or diarrhoea recorded in the toxicity studies in NHP and dogs.	In patients, the most common gastrointestinal disorders were nausea, decreased appetite, vomiting, constipation, and diarrhoea, as commented on above under clinical signs and body weight.
Liver	
In rats, lurbinectedin induced bile duct damage associated with oedema in the portal tract, cholangitis and/or bile duct proliferation/hyperplasia and periportal fibrosis, as well as hepatocellular degeneration/apoptosis and periportal hepatocytic hypertrophy. In NHP and dogs, hepatic alterations were absent and/or sporadic with no dose-relationship; there was much more limited inflammatory cell foci and reduced cellularity in the liver of some NHP.	In the ISA population, ALT increase (all grades) occurred in 65.6% of patients, reaching grade ≥3 in 6.4%. AST increase was less common: it was found in 52.7% of patients (all grades) and reached grade ≥3 in 3.3%). Alkaline phosphatase (AP) increases (regardless of relationship) occurred in 45.6% of patients (all grades) and were grade ≥3 in 4.5%. Bilirubin increases (regardless of relationship) were found in 11.8% of patients (all grades); it reached grade ≥3 in 13 patients (2.4%), however, of the 13 patients with grade ≥3 bilirubin increase, five had biliary tract carcinoma, three had bile duct obstruction (including one with liver metastasis), two had liver metastasis, one had concomitant sepsis, one had worsening pre-existing thrombus in the hepatic portal vein, and one had a tumour lesion in the hepatic hilum and treatment-related grade 4 cholangitis. No Hy's Law cases, as defined in the FDA's Guidance for Industry: Drug-Induced Liver

(from non-clinical studies)	Relevance to human usage
	Injury: Premarketing Clinical Evaluation, were found in this population. In the PM1183-B-005-14 SCLC population, ALT increase (all grades) occurred in 71.8% of patients and were grade 3 in 3.9%. AST increase (all grades) was found in 44.7% of patients and reached grade 3 in 2 patients (1.9%). AP increases (regardless of relationship) occurred in 33% of patients (all grades). Three patients had grade 3 AP increase during treatment with lurbinectedin; two of these patients already had grade 1/2 AP increase at baseline, and the third patient had liver metastases. Bilirubin increases (regardless of relationship) were found in 9.7% of patients (all grades) and were all grade 1/2.
Kidney	
In rats and dogs (at MTD and above) cortical tubular degeneration and vacuolation and tubular necrosis were observed in some animals, particularly after single dose lurbinectedin administration.	In patients treated with lurbinectedin, findings associated with renal impairment and/or kidney damage were scarcely reported, and all the episodes of grade 3 acute kidney injury or renal failure were related to the underlying malignant disease. In the ISA population, the most common biochemical abnormality (regardless of relationship) during treatment was creatinine increase according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4 (84.2% of patients [all grades]; grade ≥3 in 1.6% only). Of note, the percentage of patients with creatinine increase was lower when creatinine levels were evaluated according to the NCI-CTCAE v.3 (25.9% [all grades]; grade ≥3 in 1.1% only). Most episodes of creatinine increase during treatment were non-clinically significant, and the observed high rate of abnormalities was mainly due to the definition of grade 1 or 2 creatinine increase in NCI-CTCAE v.4 (in which normal creatinine values are considered grade 1 or 2). In the PM1183-B-005-14 SCLC population, the most common biochemical abnormality (regardless of relationship) during treatment was creatinine increase according to NCI-CTCAE v.4 (82.7% of patients; all grade 1 or 2). Of note, the percentage of patients with creatinine increase was lower when creatinine levels were evaluated according to the NCI-CTCAE v.3 (25.0%; all grade 1 or 2). Most episodes of creatinine increase during treatment were non-clinically significant, and the observed high rate of abnormalities is mainly due to the definition of grade 1 or 2 creatinine increase in NCI-CTCAE v.4.
Local tolerance	
Dose-related diffuse oedema associated with acute inflammatory reaction and necrosis were seen in male New Zealand White rabbits after i.v. and perivascular single dose administration of lurbinectedin. In repeated dose toxicity studies, irritation at the injection was regularly reported, in all species tested.	A low percentage of patients (4.7% in the ISA population and 6.7% in the PM1183-B-005-14 SCLC population) had injection site reactions.
Reproductive/developmental toxicity	

(from non-clinical studies)	Relevance to human usage
In pregnant rats, lurbinectedin induced maternal toxicity at the single dose MTD level of 0.1 mg/kg (0.6 mg/m^2) administered on Day 10 post-coitum (as shown by clinical signs and decreases in body weight, body weight gain and food consumption), and severe embryo-toxicity, leading to 100% embryo lethality.	No clinical data on exposed pregnancies are available. In accordance with oncology guidelines, no specific studies were conducted to assess fertility with lurbinectedin, and no clear signals of toxicity of reproductive organs were observed in toxicity studies. However, the nature of the compound (cytotoxic and mutagenic) suggests that it is likely to affect the reproductive capacity. Female patients receiving lurbinectedin-based therapy must agree to use a highly effective contraception methods during their treatment, and for at least seven months after the administration of the last dose. Male patients with pregnant or non-pregnant women of childbearing potential partners receiving lurbinectedin-based therapy must agree to use condom during their treatment, and for at least four months after the administration of the last dose. For a non-pregnant woment of childbearing potential partner highly effective contraception should be also advised for the same period. Embryo-foetal toxicity has been considered an important potential risk.
Potential effect on fertility	
Repeat-dose toxicity studies with lurbinectedin were conducted in rats (4 and 8 cycles), dogs (4 cycles) and NHP (4 and 8 cycles). In these experiments, each lurbinectedin cycle was defined as a bolus i.v. dose once every 3 weeks. In rats, following 4 cycles of lurbinectedin, histopathological evaluations done on Day 85 (terminal sacrifice) revealed mild oligospermia and testicular atrophy in 1 out of 7 male rats, treated at 1.08 mg/m^2, a dose level which was above the MTD in this gender (0.36 mg/m^2). No changes were recorded on Day 67 (interim sacrifice; n=10) or in animals prematurely euthanized (n=2). As a summary, histopathology alterations in testicular tissue following 4 cycles of lurbinectedin were seen in 1 out of 19 male rats treated at 1.08 mg/m^2. In the 8-cycle study in rats, histopathological examinations carried out on Day 151 (interim sacrifice), demonstrated oligospermia and testicular atrophy in 1 out of 20 male rats treated at 0.36 mg/m^2 (MTD). In dogs, following the administration of 4 cycles of lurbinectedin, slight and mild tubular cell degeneration was seen in dogs treated at 0.19 mg/m^2 (1 out of 3) and 0.58 mg/m^2 (1 out of 3) respectively, during histopathological examinations performed on Day 66 (interim sacrifice). On Day 81 (terminal sacrifice), 1 out of 3 animals treated at 0.058 mg/m^2 also had slight tubular cell degeneration. As a summary, findings (slight or/and mild tubular cell degeneration) were recorded in 3 out of 18 dogs treated at any dose level of lurbinectedin. No conclusive results may be gathered from the experiments carried out in NHP, owing to the testes immaturity in the majority of animals treated in these experiments.	Lurbinectedin targets cells that are rapidly dividing (e.g., bone marrow), as demonstrated in the general toxicity evaluation performed in animals. Moreover, the nature of the compound (cytotoxic and mutagenic) suggests that it is likely to affect the reproductive capacity. As a consequence, the findings on the potential effect on fertility seen in rat and dogs, although sporadically, are very likely related to lurbinectedin treatment. Therefore, lurbinectedin may potentially affect fertility in human.

(from non-clinical studies)	Relevance to human usage
Genotoxicity studies	
Clear positive genotoxicity results were obtained *in vitro* in mammalian cell lines, although Ames reverse mutation assays in bacteria were negative, likely due to lurbinectedin's inability to efficiently cross the bacterial wall.	It should be noted that, positive genotoxicity findings are expected with DNA-interacting antineoplastic agents, and generally considered a cautiously acceptable characteristic of agents intended for the treatment of cancer, particularly in patients with advanced or metastatic disease, that have failed previous therapies and having a limited life expectancy.
General Safety pharmacology	
The safety pharmacology evaluation of lurbinectedin has involved both *in vitro* (human Ether-à-go-go-Related Gene [hERG] assay) and *in vivo* Good Laboratory Practice studies (cardiovascular, respiratory and CNS function). *In vitro* studies Changes in hERG tail currents were measured after HEK293 cells stably transfected with hERG cDNA were exposed for 10 minutes to increasing lurbinectedin concentrations (300, 1,000, 3,000, 10,000 and 30,000 nM). The observed inhibitory concentration $(IC)_{50}$ value of 8,800 nM (~6,900 ng/mL) was more than 40-fold higher than the maximum concentration (C_{max}) (~130 ng/mL) in patients.	The discussions of relevance to human usage are provided under specific topic headings.
Cardiovascular system	
In vivo studies (Dogs) The effect of a single bolus injection of lurbinectedin on cardiovascular parameters, namely arterial blood pressure (ABP), heart rate and lead II ECG has been evaluated in conscious, telemetered dogs for a 6-hour period. No effects on heart, blood pressure, lead II ECG variables (PR, QT, QTcF and QTcV intervals, and QRS duration), ECG gross morphology or rhythm were caused in dogs dosed with lurbinectedin up to 0.01 mg/kg (0.2 mg/m^2). When dogs received a 0.023 mg/kg (0.46 mg/m^2) dose, a short-lasting tachycardia (mean increase of 89% after 1 min, followed by a rapid normalization) was recorded during the first 30 min post-administration. Although a direct pharmacological effect of lurbinectedin cannot be completely ruled out, other contributing factors to an increase in heart rate should be considered, such as lurbinectedin-induced vomiting episodes (3 out of 4 animals), which may be especially relevant in a sequential, dose-increase design as used in this study. *In vivo* studies in NHP The main clinical signs associated with lurbinectedin treatment were emesis, liquid faeces, lack of appetite, body weight decreases, as well as redness at the injection site. Also, 1 male experienced nose bleeding and decreased activity on days 11 to 13 post-dose; all these signs were normalized by Day 15. During the first 24 h post-dose interval, lurbinectedin treatment induced significant ($p \leq 0.001$ vs. placebo) fluctuations in the mean ABP (up to 15% at 3 h; up to -16% at 20 h), systolic blood pressure (up to 14% at 3 h; up to -15% at 22 h) and diastolic blood pressure (up 17% at 3 h; up to -20% at 18 h), followed by decreases ($p \leq 0.001$ vs.	Lurbinectedin at the recommended dose and schedule (3.2 mg/m^2 q3wk) did not cause clinically relevant QTcF prolongation or change in cardiac function.

(from non-clinical studies)	Relevance to human usage
placebo) in the interval from 24 to 48 h post-dose: mean ABP (up to -18% at 29 h), systolic blood pressure (up to -16% at 27.75 h) and diastolic blood pressure (up -20% at 19 h). Increases in heart rate were also noticed, the highest being +42% at 24.5 h post-dose of lurbinectedin ($p \leq 0.001$ vs. placebo). Other findings were the absence of body temperature decreases during the night as well as ST segment depression (up to +70% at 3 h; $p \leq 0.001$ vs. placebo), the latter probably being related to the increase recorded in heart rate. Also, minimal and reversible reductions ($p \leq 0.001$ vs. placebo) on PQ and PR intervals (up to -15% and +12%, respectively), the nadir being recorded at 3 h after the compound administration. A long-lasting decrease in QT interval duration (up to -14% at 11 h) was also recorded with no changes in corrected QTc and QT shift. Regarding the autonomic balance, a long-lasting decrease in heart rate high frequency oscillations amplitude from 2 to 24 h post-dose was seen (maximum -56% at 19 h; $p \leq 0.001$ vs. placebo), this effect being most likely related to a parasympathetic withdrawal as suggested by decreases in high frequency power spectral values. As a summary, lurbinectedin administered at MTD by the i.v. route to NHP induced changes to ABP and heart rate with changes in autonomic balance, most likely due to the main lurbinectedin-induced clinical signs, such as nausea and/or vomiting.	
Respiratory function	
Results showed no significant changes either in the respiratory rate (both genders) or in the tidal volume up to 24 h after lurbinectedin administration at MTD in female rats (0.6 mg/m^2). In male rats, lurbinectedin dosed at MTD (1.2 mg/m^2) caused a significant decrease in tidal volume compared to the placebo group (mean± standard deviation: 1.62±0.12 mL vs. 2.18±0.19 mL) at 24 h post-dose.	No relevant respiratory events occurred in clinical setting for which there was adequate evidence of an association with lurbinectedin. Respiratory disorders (all grades), such as dyspnoea and cough, were more frequently observed in the PM1183-B-005-14 SCLC population (30.5% and 18.1% respectively), as expected considering that these events are disorders usually associated with the underlying disease.
Central nervous system and general behaviour	
Results showed that no significant gross behavioural or physiological changes were caused in rats dosed with lurbinectedin up to MTD levels in both genders.	In patients, no relevant clinical signs associated with CNS disorders were recorded.
Drug-drug interactions	
The microsomal-mediated metabolism of lurbinectedin in various species (human included) was very intensive, due to the Cytochrome P450 3A4 (CYP3A4) isoform. The potential displacement of plasma protein bound drugs by lurbinectedin is not likely because of the extremely low C_{max} of lurbinectedin in plasma of patients (~130 ng/mL; ~150 nM) relative to the physiological levels of the binding plasma proteins. The potential of lurbinectedin to inhibit the enzymatic activities of the main Cytochrome P450 (CYP) isoforms *in vivo* is considered to be remote because the lowest estimated *in vitro* IC_{50} (~1,100 nM), is far greater than the C_{max}-values achieved in patients (~150 nM).	*Potential of other drugs to interact with lurbinectedin* In a phase I 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 a population pharmacokinetic (PK) model of lurbinectedin developed with data from 775 patients, co-administration of CYP3A4 inhibitors was found in 7% of patients and resulted in a moderate (40%) decrease in plasma clearance of lurbinectedin. Population pharmacokinetic/pharmacodynamic (PK/PD) models of the time course of absolute neutrophil count and platelets indicated that the concomitant use of CYP3A4

(from non-clinical studies)	Relevance to human usage
In primary human hepatocytes, lurbinectedin did not cause an appreciable increase in CYP1A2 and CYP3A4 activities up to 1,300 nM, suggesting limited induction potential. *In vitro* transport and intracellular accumulation experiments demonstrated that lurbinectedin is a substrate for multidrug resistance protein 1 (MDR1). Therefore, potential *in vivo* effects on the distribution of lurbinectedin upon co-administration with MDR1 modulating compounds cannot be excluded. *In vitro*, lurbinectedin may inhibit efflux (MDR1) and uptake (OATP1B1, OATP1B3 and OCT1) of human transporters. However, given the C_{max} in patients and the IC_{50} values for the affected transporters, the relevance of these findings is considered marginal.	inhibitors produced an absolute 11% and a 6.2% increase of grade 3/4 neutropenia and thrombocytopenia, respectively. *In vitro* studies on transport and intracellular accumulation indicated that lurbinectedin is likely to be a substrate for P-glycoprotein (P-gp). However, lurbinectedin is administered i.v.; so, a large effect of P-gp inhibitors/inducers on its exposure is not expected. *Potential of lurbinectedin to interact with other drugs* In a population PK model of lurbinectedin developed with data from 755 patients, co-administration of CYP3A4 inducers was found in 98% of patients, thus precluding a comparison in lurbinectedin pharmacokinetics. A recent drug-drug-interaction study with a strong CYP3A4 inhibitor (itraconazole) showed that, in comparison with lurbinectedin alone, co-administration with multiple doses of itraconazole significantly altered lurbinectedin systemic exposure reducing total plasma (by 63%) and unbound (by 58%) lurbinectedin clearance. Another drug-drug-interaction study with a moderate CYP3A4 inducer (bosentan) showed that, in comparison with lurbinectedin alone, co-administration of bosentan reduced marginally (20%) total plasma lurbinectedin systemic exposure without changes in unbound plasma lurbinectedin systemic exposure. Co-administration with bosentan increased by 25% the total plasma lurbinectedin clearance mostly by increasing its conversion to metabolite M1. The potential of lurbinectedin to inhibit the enzymatic activities of the main CYP isoforms *in vivo* is considered to be remote because the lowest estimated *in vitro* IC_{50} (1.05 mM) was in order of magnitude greater than the mean C_{max} values achieved in patients (~130 ng/mL; ~150 μM). The potential of lurbinectedin to inhibit *in vivo* any of the drug transporters evaluated, including P-gp, OATP1B1, OATP1B3 and OCT1 is considered to be remote because lowest estimated *in vitro* IC_{50} (3.85 mM) was greater than the median C_{max} observed in patients or could not be calculated due to very low maximum inhibitions achieved. A recent physiologically based pharmacokinetic (PBPK) model for lurbinectedin predict the following increase: Strong CYP3A inhibitors: coadministration of itraconazole 200 mg daily is predicted to increase lurbinectedin area under the curve (AUC) by 2.7-fold. Moderate CYP3A inhibitors: Coadministration of verapamil (80 mg every 8 hours) and erythromycin (500 mg every 6 hours) is predicted to increase lurbinectedin AUC by 2.3-fold and 2.1-fold, respectively. Weak CYP3A inhibitors: Coadministration of fluvoxamine (150 mg every 12 hours) is predicted to increase lurbinectedin AUC by 1.1-fold.

Part II: Module SIII - Clinical trial exposure

Overall, 8,489 patients have been exposed to lurbinectedin in the clinical trial program, including 2,238 in clinical trials (Table 2), 465 in Investigator initiated studies (Table 15) and 5,786 in compassionate uses.

Overview of 27 sponsored lurbinectedin clinical trials:

A summary table of the exposure to lurbinectedin for each of the 27 individual clinical studies ongoing or completed through July 29, 2024, is provided in Table 2.

Table 2. Overview of 27 sponsored lurbinectedin clinical trials

Study code (indication)	Lurbinectedin q3wk schedule	Treated patients	Status
Studies as single agent			
Phase I studies			
PM1183-A-001-08 (solid tumours)	0.02 to 5.0 mg/m^2 day (D)1 Recommended dose (RD): 7 mg flat dose (FD) D1	31	Completed
PM1183-A-002-10 (haematological)	3.5 to 7.0 mg FD D1, D8 RD not reached	24	Completed
	1.0 to 3.0 mg FD D1-D3 RD not defined	18	
PM1183-A-005-11 (solid tumours)	3.0 to 5.0 mg FD D1, D8 RD: 5 mg FD D1, D8	21	Completed
PM1183-A-013-15 (solid tumours)	1.5 to 3.2 mg/m^2 without Granulocyte Colony-Stimulating Factor (G-CSF) 3.2 to 3.5 mg/m^2 with G-CSF	26	Completed
PM1183-A-015-16 (mass balance)	First cycle: 5 mg D1 Other cycles: 3.2 mg/m^2 D1	6	Completed
PM1183-A-017-20 (solid tumours, hepatic impairment)	Normal hepatic function cohort: 3.2 mg/m^2, D1 Hepatic impairment (HI) cohorts: Mild HI: 3.2 mg/m^2, D1 Moderate HI: 1.6 mg/m^2, D1 Severe HI: 1.6 mg/m^2, D1	32[a]	Completed
LY01017/CT-CHN-101 (solid tumours)	2.5 mg/m^2 to 3.2 mg/m^2 D1 q3wk	32	Completed
Phase II studies			
PM1183-B-001-10 (pancreatic cancer)	7.0 mg FD D1	44	Completed
PM1183-B-002-11 (platinum resistant/refractory ovarian cancer)	7.0 mg FD D1	52	Completed
	7.0 mg FD D1 after crossover from topotecan	15	
PM1183-B-003-11 (breast cancer)	7.0 mg FD or 3.5 mg/m^2 D1	109	Completed
PM1183-B-004-13 (non-small cell lung cancer)	7.0 mg FD or 3.2 mg/m^2 D1	21	Completed
	3.0 mg duration of response or 1.6 mg/m^2 D1 + gemcitabine 800 mg/m^2 D1, D8 q3wk	25	
PM1183-B-005-14 (solid tumours including SCLC)	3.2 mg/m^2 D1	335[b]	Completed

Study code (indication)	Lurbinectedin q3wk schedule	Treated patients	Status
PM1183-B-005-QT	3.2 mg/m^2 D1	39	Completed
JZP712-201: EMERGE-201	3.2 mg/m^2 on Day 1 of q3w cycle	47	Ongoing
JZP712-101: EMERGE-101 (relapsed/refractory Ewing sarcoma)	Lurbinectedin monotherapy: • Dose Level -1: 2.6 mg/m^2 q3wk • Dose Level 0 (starting dose): 3.2 mg/m^2 q3wk • Dose Level +1: 4.0 mg/m^2 q3wk • Dose Level +2: 5.0 mg/m^2 q3wk • Intermediate dose level (if recommended by data monitoring committee)	10	Ongoing
Phase III studies			
PM1183-C-004-14 (platinum resistant ovarian cancer)	3.2 mg/m^2 D1	219	Completed
Studies in combination with other drugs			
Phase I studies			
PM1183-A-003-10 (solid tumours)	3.0 to 5.0 mg FD D1 plus doxorubicin 50 mg/m^2 q3wk	120	Completed
PM1183-A-004-10 (solid tumours)	2.5 to 3.5 mg FD D1, D8 + gemcitabine 800 mg/m^2 q3wk RD: 3.0 mg FD (1.6 mg/m^2) D1, D8+gemcitabine 800 mg/m^2 q3wk	45	Completed
PM1183-A-006-12 (solid tumours)	2.0 to 3.0 mg FD D1, D8 + Capecitabine 1,650 mg/m^2 D1-D14 q3wk 3.0 to 5.0 mg FD or 2.8 mg/m^2 D1 + Capecitabine 1,650 or 2,000 mg/m^2 D1-D14 q3wk	81	Completed
PM1183-A-007-13 (solid tumours)	3.0 to 5.0 mg FD or 2.2 mg/m^2 D1 + Paclitaxel 60 or 80 mg/m^2 D1-D8 q3wk	55	Completed
	2.2 mg/m^2 D1 + Paclitaxel 80 mg/m^2 D1-D8 q3wk + BEV 15 mg/kg D1 q3wk	12	
PM1183-A-008-13 (solid tumours)	0.5 to 1.7 mg/m^2 D1 + cisplatin 60 mg/m^2 D1 with aprepitant 1.1 to 1.7 mg/m^2 D1 + cisplatin 60 mg/m^2 D1 q3wk without aprepitant	41	Completed
PM1183-A-014-15 (solid tumours)	1.0 to 2.0 mg/m^2 D1 + irinotecan 75 mg/m^2 D1,D8 q3wk without G-CSF 2.0 to 2.4 mg/m^2 D1 + irinotecan 75 mg/m^2 D1,D8 q3wk with G-CSF 3.0 mg/m^2 D1 + irinotecan 15 to 30 mg/m^2 D1,D8 q3wk	303	Ongoing
PM1183-A-018-20 (solid tumours, drug-drug interaction [DDI] with strong CYP3A4 inhibitor)	Itraconazole co-administration cycle: Itraconazole: 200 mg (two capsules of 100 mg) orally once daily (for 12 days) Lurbinectedin: 0.8 mg/m² D1 on Part A, dose on Part B will depend on PK and safety outcomes in Part A Single agent lurbinectedin cycle: 3.2 mg/m² D1	14	Completed

Study code (indication)	Lurbinectedin q3wk schedule	Treated patients	Status
PM1183-A-019-20 (solid tumours, DDI with moderate CYP3A4 inducer)	Bosentan co-administration cycle: Bosentan: 125 mg (one film-coated tablet of 125 mg) orally twice daily in the morning and in the evening during the prior 5 consecutive days before the day of lurbinectedin infusion (D 1), and once daily on D1 (before lurbinectedin infusion) Lurbinectedin: 3.2 mg/m² D1 in first 3 patients; dose for remaining 5 patients will depend on PK and safety outcomes in first 3 patients Single agent lurbinectedin cycle: 3.2 mg/m² D1	11	Completed
Phase III studies			
PM1183-C-003-14 (SCLC)	2.0 mg/m^2 D1 + doxorubicin 40 mg/m^2 q3wk	304[d]	Completed
PM1183-C-008-21 (SCLC)	Group A: Lurbinectedin 3.2 mg/m^2 as a 60-min infusion on D1 q3wk Group B: Irinotecan 75 mg/m^2 as a 90-min infusion on D1 q3wk followed by lurbinectedin 2.0 mg/m^2 as a 60-min infusion on D1 q3wk, with G-CSF	335[b]	Ongoing
GO43104/IMforte (ES-SCLC)	Induction phase: Atezolizumab on D1 q3wk in combination with carboplatin on D1 and etoposide on D1, D2, and D3 q3wk for 4 cycles. Maintenance phase: Atezolizumab on D1 q3wk in combination with lurbinectedin on D1 q3wk.	242	Ongoing
PM1183-C-010-22 (Leiomyosarcoma)	Patients will receive the following on Day 1 q3wk: Experimental Arm A: • Doxorubicin: i.v. push or bolus (according to label) of 50 mg/m^2 followed by • Lurbinectedin: i.v. 1-hour infusion of 2.2 mg/m^2. Experimental Arm B: • Doxorubicin: i.v. push or bolus (according to label) of 25 mg/m^2 followed by • Lurbinectedin: i.v. 1-hour infusion of 3.2 mg/m^2.	38[b]	Ongoing

Cut-off date: July 29, 2024. Only arms with patients treated with lurbinectedin are shown. In all studies, lurbinectedin was administered as a 1-hour i.v. infusion.

a This study was completed on 29 April 2024 and the clinical study report was issued on 18 September 2024, during the preparation of this RMP, and therefore, the study appears as completed.

b These numbers have not been added to the total number of subject exposure to lurbinectedin since they belong to clinical trials for which data are blinded for statistical analysis.

c Thirty-nine patients from study PM1183-B-005-14 were also included in the study PM1183-B-005-QT, which evaluated QT in ECG of patients with normal cardiac conduction and function, systolic blood pressure of 90-150 mmHg and normal serum electrolyte levels. These patients received two cycles under PM1183-B-005-QT and subsequent cycles were evaluated in PM1183-B-005-14.

d Includes 2 patients enrolled into study PM1183-C-003-14 and randomized to the Control arm (cyclophosphamide, doxorubicin, and vincristine [CAV] or topotecan) who, due to a mistake, received one cycle each of Lurbinectedin + doxorubicin.

D, day; ECG, electrocardiogram; FD, flat dose; G-CSF, granulocyte colony- stimulating factor; HI, hepatic impairment; i.v., intravenous; q3wk, every three weeks; RD, recommended dose; SCLC, small cell lung cancer.

Cumulative exposure figures are presented for all indications by duration, age group and sex, dose and ethnic origin in Table 3, Table 4, Table 5 and Table 6, respectively.

Table 3. Duration of exposure for all indications

Duration of exposure	Patients	Person-months
>0 m and <1 month	215	211.9
≥1 month	2,023	10,862.6
≥3 months	1,248	9,357.0
≥6 months	622	6,709.7
≥9 months	296	4,342.9
≥12 months	143	2,764.1
≥15 months	97	2,151.1
≥18 months	69	1,689.1
≥21 months	40	1,128.1
≥24 months	24	770.8
Total	**2,238**	**11,074.5**

Table 4. Exposure by age group and sex for all indications

Age group	Patients		Person-months	
	Male	Female	Male	Female
18 - 54 years	222	376	774.4	1,735.0
55 - 64 years	362	470	1,973.5	2,467.2
65 - 74 years	307	373	1,444.0	2,141.2
≥75 years	73	55	269.8	269.2
Total	**964**	**1,274**	**4,461.8**	**6,612.7**

Table 5. Exposure by dose for all indications

Dose of exposure	Patients	Person-months
3.2 mg/m²	877	4,280.2
7.0 mg FD	220	817.9
Other	1,141	5,976.3
Total	**2,238**	**11,074.5**

Table 6. Exposure by ethnic origin for all indications

Ethnic origin	Patients	Person-months
Asian	108	499.7
Black	32	109.9
White	1,859	9,494.9
Other	20	78.2
Unknown	219	891.8
Total	**2,238**	**11,074.5**

The safety of single agent lurbinectedin was evaluated in a phase II open-label study in patients with selected advanced solid tumours (PM1183-B-005-14) and one phase III randomised study versus pegylated liposomal doxorubicin (PLD) or topotecan in patients with platinum-resistant ovarian cancer (PM1183-C-004-14). The ISA included 554 patients from these 2 studies who received lurbinectedin at the recommended dosing regimen of 3.2 mg/m^2 every 21 days. These patients included 105 with SCLC, 230 patients with various cancers (endometrial carcinoma [n=73], neuroendocrine tumours [n=32], Ewing's family of tumours [n=28], germ cell tumours [n=23], breast cancer gene (BRCA) 1/2-associated metastatic breast carcinoma [n=21], biliary tract carcinoma [n=19], carcinoma of unknown primary site [n=19], and head and neck carcinoma [n=15]) and 219 ovarian cancer patients from the lurbinectedin arm of study PM1183-C-004-14.

Cumulative lurbinectedin exposure in 105 SCLC patients from study PM1183-B-005-14 are presented by duration, age group and gender, dose and ethnic origin in Table 7, Table 8, Table 9 and Table 10, respectively.

Table 7. Duration of exposure for SCLC indication (PM1183-B-005-14)

Duration of exposure	Patients	Person-months
>0 m and <1 month	10	9.9
≥1 month	95	491.5
≥3 months	65	435.0
≥6 months	30	290.9
≥9 months	12	158.9
≥12 months	6	99.2
≥15 months	5	86.3
≥18 months	1	19.5
Total	**105**	**501.3**

Table 8. Exposure by Age group and gender for SCLC (PM1183-B-005-14)

Age group	Patients		Person-months	
	Male	Female	Male	Female
18 - 54 years	17	11	59.1	46.9
55 - 64 years	22	18	141.9	105.5
65 - 74 years	17	11	75.5	32.2
≥75 years	7	2	23.7	16.5
Total	**63**	**42**	**300.2**	**201.1**

Table 9. Exposure by dose for SCLC (PM1183-B-005-14)

Dose of exposure	Patients	Person-months
3.2mg/m²	105	501.3
Total	**105**	**501.3**

Table 10. Exposure by ethnic origin for SCLC (PM1183-B-005-14)

Ethnic origin	Patients	Person-months
Asian	1	1.9
Black	1	1.7
White	79	410.2
Unknown	24	87.5
Total	**105**	**501.3**

The safety of lurbinectedin in combination with atezolizumab was evaluated in a phase III open-label study in 242 patients with ES-SCLC (IMforte, GO43104). Cumulative exposure in these 242 patients are presented by duration, age group and gender, dose and ethnic origin in Table 11, Table 12, Table 13 and Table 14, respectively.

Table 11. Duration of exposure for persons included in IMforte

Duration of exposure	Patients	Person-months
>0 m and <1 month	13	12.8
≥1 month	229	1,474.8
≥3 months	178	1,371.6
≥6 months	98	1,024.7
≥9 months	53	694.1

Duration of exposure	Patients	Person-months
≥12 months	24	397.8
≥15 months	14	266.2
≥18 months	9	183.0
≥21 months	3	69.2
Total	**242**	**1,487.6**

Table 12. Exposure by age group and sex for persons included in IMforte

Age group	Patients		Person-months	
	Male	Female	Male	Female
18 - 54 years	10	5	43.4	21.6
55 - 64 years	62	42	431.7	265.1
65 - 74 years	58	38	359.7	227.3
≥75 years	21	6	105.8	33.1
Total	**151**	**91**	**940.5**	**547.1**

Table 13. Exposure by dose for persons included in IMforte

Dose of exposure	Patients	Person-months
3.2 mg/m²	242	1,487.6
Total	**242**	**1,487.6**

Table 14. Exposure by ethnic origin for persons included in IMforte

Ethnic origin	Patients	Person-months
Asian	31	193.4
Black	3	34.0
White	195	1,197.5
Other	1	10.0
Unknown	12	52.8
Total	**242**	**1,487.6**

Overview of Investigator initiated studies (IIS):

As of 29 July 2024, 11 IIS have been conducted with lurbinectedin.

Table 15: Cumulative Subject Exposure to Lurbinectedin in IISs

IIS	Description	Exposure
LUPER (MedOPP300)	Sponsored by Dr. Antonio Calles Blanco (Hospital General Universitario Gregorio Marañón, Spain) and conducted in Spain. It is a multicentre, Phase I-II pharmacokinetic study investigating lurbinectedin in combination with pembrolizumab in patients with relapsed SCLC.	28
2SMALL (PM1183-A-020-17)	Sponsored by Fundación Oncosur in Spain. It is a multicentre, Phase I-II study investigating lurbinectedin in combination with atezolizumab in patients with advanced SCLC that had progressed following prior therapy with platinum-based chemotherapy.	171
IST-2021-MCC-20332	Dr. Chiappori study, sponsored by H Lee Moffitt Cancer Centre and Research Institute in the United States (US). It is a single site, single arm, Phase I-II study investigating the MTD, recommended phase II dose (RP2D) and the safety and efficacy of the combination of nivolumab-ipilimumab plus lurbinectedin in patients with SCLC after progression with first line, platinum-based chemotherapy (relapsed/recurrent SCLC).	9
SAKK 17/16	Sponsored by the Swiss Group for Clinical Cancer Research (SAKK) in Switzerland. It is a multicentre, single-arm, Phase II study in patients with progressive malignant pleural mesothelioma.	42

IIS	Description	Exposure
IST15083	Conducted in the US. The study investigated lurbinectedin either as a single agent, or in combination with either gemcitabine or doxorubicin, in metastatic and/or unresectable sarcomas.	42
POLA/ACOG1401	Conducted in Spain. The study investigated lurbinectedin in combination with olaparib in subjects with advanced solid tumours.	93
IST-HIGGINS-RAD5466-21	Conducted in the US. This is a phase I study of palliative radiotherapy with lurbinectedin in patients with extensive stage SCLC.	14
IST-COTE-21-437	Conducted in the US. The study investigated lurbinectedin plus doxorubicin in leiomyosarcoma	42*
IST- BORAZANCI-HRI-21	Conducted in the US. The study investigated lurbinectedin in patients with advanced pancreatic cancer with DNA repair mutations	7
IST- Westin-2022-0231-LUR	Conducted in the US. The study investigated lurbinectedin in combination with weekly paclitaxel and bevacizumab	6
IST-GORDON-SOC-2310-LUR	Conducted in the US. The study investigated lurbinectedin in combination with ipilimumab, and nivolumab for advanced soft tissue sarcomas	11
Total		**465**

*Data available as of 14 June 2024

DNA, deoxyribonucleic acid; MTD, maximum tolerated dose; RP2D, recommended phase II dose; SAKK, Swiss Group for Clinical Cancer Research; SCLC, small cell lung cancer; US, United States (of America).

Individual patient use:

As of 29 July 2024, 5,786 patients have been treated with lurbinectedin in early access programs or individual compassionate use.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The important exclusion criteria from lurbinectedin monotherapy and in combination with atezolizumab are discussed below.

Important exclusion criteria from lurbinectedin monotherapy:

The important exclusion criteria from the phase II study PM1183-B-005-14A (advanced solid tumours including SCLC) and phase III study PM1183-C-004-14 (ovarian cancer) are discussed below.

Exclusion Criterion: Age <18 years

Reason for exclusion:

SCLC is primarily a disease of elderly people with history of long-term tobacco exposure (4).

Is it considered to be included as missing information? No

Rationale:

SCLC is diagnosed most frequently in elderly patients and it rarely occurs in patients aged less than 45 years old (4).

Exclusion Criteria: Haemoglobin <9 g/dl, absolute neutrophil count (ANC) <2.0×10^9/L; and platelet count <100×10^9/L.

Reason for exclusion:

Patients with laboratory values meeting the criteria above were excluded from the phase II and phase III studies for safety reasons because slight to moderate anaemia, thrombocytopenia and marked and dose-related reticulopenia and leukopenia was observed in non-clinical studies. In addition, myelosuppression, consisting mostly of grade 3/4 neutropenia and thrombocytopenia, was observed in single-agent phase I studies.

Is it considered to be included as missing information? No

Rationale:

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of lurbinectedin. The reference safety information warns to monitor full blood counts including differential white blood cells and platelet count at baseline and prior to each cycle. Dose instructions specify to initiate treatment with lurbinectedin only if absolute neutrophil count is at least 1.5 x 10^9/L and platelet count is at least 100×10^9/L.

Exclusion Criteria: ALT and AST >3.0×upper limit of normal (ULN); Total bilirubin >1.5×ULN, or direct bilirubin >ULN; AP >5.0×ULN; Albumin <3 g/dL.

Reason for exclusion:

Patients with laboratory values meeting the criteria above were excluded from the phase II and phase III studies for safety reasons. Significant increases in liver function tests, hepatocellular necrosis and biliary damage were observed in non-clinical studies mainly at or above the MTD. In addition, mainly mild asymptomatic transaminase increases were observed in phase I studies at the recommended dose, none of which were associated with bilirubin increases and all patients recovered. All transaminase increases were transient.

Is it considered to be included as missing information? No.

Rationale:

Patients with severe hepatic impairment (ALT and AST >3.0×ULN; Total bilirubin >1.5×ULN, or direct bilirubin >ULN) were excluded from the phase II and phase III studies. Based on population pharmacokinetic analysis, no apparent pharmacokinetic difference was observed in 125 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin between 1.0-1.5xULN and any AST) who received lurbinectedin 3.2 mg/m² every 21 days as compared to 625 patients with normal hepatic function.

A dedicated study was conducted to evaluate the influence of varying degrees of hepatic impairment on lurbinectedin in patients with advanced solid tumors. Patients with normal hepatic function and those with mild hepatic impairment (total bilirubin ≤1×ULN and AST >1×ULN, or total bilirubin > 1 to ≤1.5×ULN and AST = any) received lurbinectedin at a dose of 3.2 mg/m^2. Patients with moderate hepatic impairment (total bilirubin >1.5 to ≤3×ULN and AST = any) or severe hepatic impairment (total bilirubin >3×ULN) were dosed at 1.6 mg/m² of lurbinectedin. *Mild hepatic impairment:* Following administration of 3.2 mg/m^2 in patients with mild hepatic impairment (n=9), no clinically significant differences in the pharmacokinetics of lurbinectedin were identified in patients with mild hepatic impairment. *Moderate hepatic impairment:* Following administration of 1.6 mg/m^2 in patients with moderate hepatic impairment (n=8), a 23% decrease in dose-normalized AUC was observed compared to patients with mild hepatic impairment (n=9) (ratio: 0.77, 90% CI: 0.47–1.28). *Severe hepatic impairment:* Following administration of 1.6 mg/m^2 in patients with severe hepatic impairment (n=6), a 16% increase in dose-normalized AUC was observed compared to patients with mild hepatic impairment (n=9) (ratio: 1.16, 90% CI: 0.67-2.00). A substantial inter-individual variability was observed in most pharmacokinetic parameters, due to the inter-individual variability of the pharmacokinetics observed and the limited data on this population, a dose modification could not be determined in patients with severe hepatic impairment.

Exclusion criterion: Chronic active hepatitis or cirrhosis

Reason for exclusion:

Patients with chronic active hepatitis or cirrhosis may be at increased risk and would confound safety assessments.

Is it considered to be included as missing information? No

Rationale:

A dedicated study (PM1183-A-017-20) was conducted to evaluate the influence of varying degrees of hepatic impairment on lurbinectedin in patients with advanced solid tumors.

Exclusion Criteria: Serum creatinine >1.5×ULN or creatinine clearance (CrCl) <30 ml/min

Reason for exclusion:

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

Is it considered to be included as missing information? No

Rationale:

Urinary excretion is a minor route of elimination for lurbinectedin with only 6% of a radioactive dose recovered in the urine. According to the reference safety information, no dose adjustment is recommended in patients with mild (CrCl 60-89 mL/min) or moderate (CrCl of 30-59 mL/min) renal impairment. As lurbinectedin has not been evaluated in a sufficient number of patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease to estimate the risk, the reference safety information advises that it should only be used with caution and careful monitoring in these patients and to not administer lurbinectedin to patients with calculated creatinine clearance less than 30 mL/min. This advice is considered sufficient, given that renal excretion is only a minor route of excretion.

Exclusion criterion: Creatine phosphokinase (CPK) >2.5×ULN.

Reason for exclusion:

Subjects with abnormal CPK values as defined above were excluded for safety reasons and to reduce potential confounders relating to safety assessments concerning muscle toxicity. One case of lurbinectedin-related grade 4 rhabdomyolysis (in association with CPK increase) was reported in the phase I leukaemia study as a dose-limiting toxicity at the 6.0 mg/m^2 dose.

Is it considered to be included as missing information? No

Rationale:

The reference safety information advises to withhold the dose of lurbinectedin if grade 2 rhabdomyolysis occurs until grade ≤1 and resume at the same dose. If grade ≥3 rhabdomyolysis occurs lurbinectedin should be permanently discontinued.

Exclusion Criteria:

- ***Prior or concurrent malignant disease unless in complete remission for more than five years, except treated in situ carcinoma of the cervix, basal or squamous cell skin carcinoma, and in situ transitional cell bladder carcinoma (PM1183-B-005-14A).***
- ***History of another neoplastic disease (except for curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, or properly treated carcinoma in situ of the uterine cervix or breast) within three years prior to randomization (PM1183-C-004-14).***

Reason for exclusion:

To reduce confounding factors due to prior or concurrent malignant disease in the safety and efficacy assessments.

Is it considered to be included as missing information? No

Rationale:

These exclusion criteria are not pertinent to the post-marketing setting. No specific safety concerns with respect to the use of lurbinectedin in these patients are anticipated.

Exclusion Criteria: Known CNS involvement. In patients with SCLC, brain computed tomography (CT)-scan or magnetic resonance imaging (MRI) results must be provided at baseline / Known brain metastases or leptomeningeal disease involvement.

Reason for exclusion:

To avoid confounders in efficacy and safety assessments due to the presence of pre-existing brain metastases.

Is it considered to be included as missing information? No

Rationale:

No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

Exclusion Criteria:

- ***History, within the last year, or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically relevant valvular heart disease or symptomatic arrhythmia or any asymptomatic ventricular arrhythmia requiring ongoing treatment (PM1183-B-005-14).***
- ***History of cardiac disease: myocardial infarction or symptomatic/uncontrolled angina within the year prior to enrolment; or congestive heart failure defined as abnormal left ventricular ejection fraction (LVEF) <50% assessed by multiple-gated acquisition scan or equivalent by ultrasound; or symptomatic arrhythmia (PM1183-C-004-14).***

Reason for exclusion:

Patients with the above cardiovascular conditions may be at increased risk and would confound the efficacy and safety assessments.

Is it considered to be included as missing information? No

Rationale:

These exclusion criteria are not pertinent to the post-marketing setting. No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

Exclusion criterion: Grade ≥3 dyspnoea or daily intermittent oxygen requirement within two weeks prior to the study treatment onset.

Reason for exclusion:

Patients with severe dyspnoea or requiring oxygen may be at increased risk and would confound the efficacy and safety assessments.

Is it considered to be included as missing information? No

Rationale:

These exclusion criteria are not pertinent to the post-marketing setting. No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

Exclusion Criteria:

- ***Active infection/Active uncontrolled infection.***
- ***Unhealed wounds or presence of any external drainage/ Requirement of permanent or frequent (i.e., once per week) external drainages within two weeks prior to randomization.***

Reason for exclusion:

As lurbinectedin may cause myelosuppression, there is an increased risk of infection. Hence, patients meeting the above criteria were excluded to avoid confounders due to pre-existing infection or the presence of pre-existing risk factors for infection (e.g., external drainage).

Is it considered to be included as missing information? No

Rationale:

The reference safety information warns about the risk of bone marrow suppression and to monitor blood counts including neutrophil count and platelet count prior to each administration.

Exclusion criterion: Immunocompromised patients, including known infection by human immunodeficiency virus (HIV).

Reason for exclusion:

For safety reasons, since immunocompromised patients and patients with HIV may be at increased risk of contracting infections.

Is it considered to be included as missing information? No

Rationale:

The reference safety information warns about the risk of bone marrow suppression and to monitor blood counts including neutrophil count and platelet count prior to each administration.

Exclusion criterion: Bowel obstruction (PM1183-C-004-14)

Reason for exclusion:

For safety reasons, since the presence of bowel obstruction (ovarian cancer study) would increase the patient's risk of infection and confound safety assessments.

Is it considered to be included as missing information? No

Rationale:

These exclusion criteria were in place for the sub-set of patients with ovarian cancer who are more prone to bowel obstructions than the SCLC population. Bowel obstruction may increase the risk of abdominal infection. The reference safety information warns about the risk of bone marrow suppression and to monitor blood counts including neutrophil count and platelet count prior to each administration.

Exclusion criteria: Women who are pregnant or breast feeding and fertile patients (men and women) who are not using an effective method of contraception.

Reason for exclusion:

Pregnant women were excluded from the clinical studies because there is no available data to inform about the risks of using lurbinectedin during human pregnancy. Animal studies in pregnant rats during the period of organogenesis demonstrated embryo-foetal lethality and maternal toxicity. Based on its mechanism of action, lurbinectedin may cause foetal harm when administered during pregnancy.

Breast feeding women were excluded from the clinical studies because there are no data regarding the presence of lurbinectedin in human milk, therefore, a potential risk from lurbinectedin in breastfed children could not be ruled out.

Is it considered to be included as missing information? No

Rationale:

Animal studies in pregnant rats during the period of organogenesis demonstrated embryo-foetal lethality and maternal toxicity.

Exclusion criterion: Impending need for radiotherapy (e.g., painful bone metastasis and/or risk of spinal cord compression) (PM1183-B-005-14A).

Reason for exclusion:

Radiotherapy was excluded to avoid confounders with respect to efficacy and safety assessments. Therefore, patients with an impending need for radiotherapy were excluded from the study.

Is it considered to be included as missing information? No

Rationale:

These exclusion criteria are not pertinent to the post-marketing setting. No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

Important exclusion criteria from lurbinectedin in combination with atezolizumab:

The exclusion criteria below correspond to the maintenance phase of study GO43104 (IMforte) for the combination of lurbinectedin and atezolizumab. Participants are excluded from randomization in the study if any of the following main criteria apply after completion of the induction phase:

Exclusion criterion: Haemoglobin <9 g/dl, ANC <1.5×10^9/L of non-African descendent or ANC <1.3·10^9/L of African descent without G-CSF support, Lymphocyte count <0.5·10^9/L and platelet count <100×10^9/L without transfusion.

Reason for exclusion:

Patients with laboratory values meeting the criteria above were excluded for safety reasons because slight to moderate anaemia, thrombocytopenia and marked and dose-related reticulopenia and leukopenia was observed in non-clinical studies for lurbinectedin.

Is it considered to be included as missing information? No

Rationale:

Bone marrow suppression (primarily neutropenia) is a dose-limiting toxicity of lurbinectedin. The reference safety information warns to monitor full blood counts including differential white blood cells and platelet count at baseline and prior to each cycle.

Exclusion criterion: ALT, AST and AP >2.5× ULN, Total bilirubin >1.5×ULN; Albumin <3 g/dL; Creatinine >1.5·ULN or CrCl <30 mL/min and CPK >2.5×ULN.

Reason for exclusion:

Patients with laboratory values meeting the criteria above were excluded for safety reasons. Significant increases in liver function tests, hepatocellular necrosis and biliary damage were observed in non-clinical studies for lurbinectedin mainly at or above the MTD. In addition, mainly mild asymptomatic transaminase increases were observed in lurbinectedin phase I studies at the recommended dose, none of which were associated with bilirubin increases and all patients recovered. All transaminase increases were transient.

Is it considered to be included as missing information? No.

Rationale:

The reference safety information indicates that liver tests, including ALT, AST and bilirubin should be monitored prior to initiating lurbinectedin and periodically during treatment as clinically indicated.

Exclusion criterion: CNS metastases.

Reason for exclusion:

To avoid confounders in efficacy and safety assessments due to the presence of pre-existing brain metastases.

Is it considered to be included as missing information? No

Rationale:

No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

Exclusion criterion: Need for consolidative chest radiation.

Reason for exclusion:

Patients that need consolidative chest radiation were excluded from the study since treatment with lurbinectedin needs to be withheld for a minimum of two weeks after the last dose of radiotherapy which was considered incompatible given the aggressive nature of the disease.

Is it considered to be included as missing information? No

Rationale:

These exclusion criteria are not pertinent to the post-marketing setting.

Exclusion criterion: Uncontrolled tumour-related pain.

Reason for exclusion:

Patients must enter the study in the best possible physical condition.

Is it considered to be included as missing information? No

Rationale:

No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

Exclusion criterion: Requirement of palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement).

Reason for exclusion:

Radiotherapy was excluded to avoid confounders with respect to efficacy and safety assessments. In addition, treatment with lurbinectedin needs to be withheld for a minimum of two weeks after the last dose of radiotherapy which was considered incompatible given the aggressive nature of the disease.

Is it considered to be included as missing information? No

Rationale:

No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

Exclusion criterion: Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium > ULN).

Reason for exclusion:

Hypercalcaemia is a sign of poor prognosis that could confound interpretation of trial efficacy data.

Is it considered to be included as missing information? No

Rationale:

Rationale is not applicable to this RMP since this exclusion criteria is applicable to the use of atezolizumab in the study.

Exclusion criterion: History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.

Reason for exclusion:

Based on the mechanism of action, it was anticipated that atezolizumab may be associated with immune-mediated adverse reactions similar to those observed in autoimmune disease as well as inflammatory lung diseases similar to interstitial lung disease. Patients with autoimmune diseases as well as inflammatory lung diseases were excluded from clinical studies as it was not known whether use of atezolizumab in these patients is associated with exacerbation of the existing autoimmune condition.

Is it considered to be included as missing information? No

Rationale:

Rationale is not applicable to this RMP since this exclusion criteria is applicable to the use of atezolizumab in the study.

Exclusion criterion: Active tuberculosis.

Reason for exclusion:

These patients were excluded to minimise the effects and possible complications of synergistic immunologic stimulation by atezolizumab and infection.

Is it considered to be included as missing information? No

Rationale:

Rationale is not applicable to this RMP since this exclusion criteria is applicable to the use of atezolizumab in the study.

Exclusion criterion: A major surgical procedure, other than for diagnosis, within 4 weeks prior to randomization into the maintenance phase, or anticipation of need for a major surgical procedure during the study.

Reason for exclusion:

To avoid complications with the immediate postoperative period.

Is it considered to be included as missing information? No

Rationale:

No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

Exclusion criterion: Severe infection within 2 weeks prior to randomization into the maintenance phase, including, but not limited to, hospitalization for complications of infection, bacteraemia, or severe pneumonia, or any active infection that could impact participant safety.

Reason for exclusion:

As lurbinectedin may cause myelosuppression, there is an increased risk of infection. Hence, patients meeting the above criteria were excluded to avoid confounders due to pre-existing infection or the presence of pre-existing risk factors for infection (e.g., external drainage).

Is it considered to be included as missing information? No

Rationale:

The reference safety information warns about the risk of bone marrow suppression and to monitor blood counts including differential white blood cells and platelet count at baseline and prior to each cycle.

Exclusion criterion: Treatment with therapeutic oral or i.v. antibiotics at the time of randomization.

Reason for exclusion:

Patients with severe active infections were excluded to minimise the effects and possible complications of synergistic immunologic stimulation by atezolizumab and infection.

Is it considered to be included as missing information? No

Rationale:

Rationale is not applicable to this RMP since this exclusion criteria is applicable to the use of atezolizumab in the study.

Exclusion criterion: Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the participant at high risk from treatment complications.

Reason for exclusion:

Patients meeting the above criteria were excluded to avoid confounders.

Is it considered to be included as missing information? No

Rationale:

No specific safety concerns relating to the use of lurbinectedin in these patients are anticipated.

SIV.2 Limitations to detect adverse reactions in clinical trial development programme

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 16. Exposure of special populations included or not in clinical trial development programmes*

Type of special population					Exposure					
Pregnant women					Not included in the clinical development programme					
Patients with relevant comorbidities:										
Patients with hepatic impairment:										
Parameter	All indications		ISA		SCLC		Patients excluded from ISA		Patients from IMforte	
	Patients	Person-months	Patients	Person-months	Patients	Person-months	Patients	Person-months	Patients	Person-months
ALT										
≤ULN	1,932	9,829.7	507	2,335.6	96	461.5	1,196	6,106.3	229	1,387.8
>ULN and ≤3.0 ULN	265	1,056.6	46	166.4	9	39.8	206	790.4	13	99.8
>3.0 ULN and ≤5 ULN	3	5.7	1	3.1	0	0	2	2.7	0	0
>5 ULN and ≤20 ULN	5	5.7	0	0	0	0	5	5.7	0	0
Missing	33	176.8	0	0	0	0	33	176.8	0	0
AST										
≤ULN	1,843	9,477.5	469	2,227.1	82	408.8	1,146	5,845.0	228	1,405.3
>ULN and ≤3.0 ULN	337	1,353.1	81	260.8	21	81.8	242	1,010.0	14	82.3
>3.0 ULN and ≤5 ULN	16	31.8	2	6.4	0	0	14	25.4	0	0
>5 ULN and ≤20 ULN	5	4.9	0	0	0	0	5	4.9	0	0
Missing	37	207.2	2	10.6	2	10.6	35	196.6	0	0
AP										
≤ULN	1,610	8,425.4	416	1,981.6	88	431.3	1,001	5,199.0	193	1,244.7
>ULN and ≤2.5 ULN	489	2,183.8	119	461.1	16	66.9	323	1,499.1	47	223.5
>2.5 ULN and≤5 ULN	63	173.9	17	49.4	1	3.1	44	105.0	2	19.4
>5 ULN and ≤20 ULN	14	26.9	2	12.8	0	0	12	14.1	0	0
Missing	62	264.6	0	0	0	0	62	264.6	0	0
Bilirubin										
≤ULN	2,142	10,720.1	541	2,464.7	103	498.7	1,361	6,779.3	240	1,476.0

>ULN and ≤1.5 ULN	45	142.2	12	37.9	2	2.7	32	103.4	1	1.0
>1.5 ULN and ≤3 ULN	11	25.4	1	2.4	0	0	9	12.4	1	10.6
>3 ULN and ≤10 ULN	5	4.9	0	0	0	0	5	4.9	0	0
>10 ULN	1	1.0	0	0			1	1.0	0	0
Missing	34	180.9	0	0	0	0	34	180.9	0	0
Total	**2,238**	**11,074.5**	**554**	**2,505.0**	**105**	**501.3**	**1,442**	**7,081.9**	**242**	**1,487.6**
Type of special population					**Exposure**					
Patients with renal impairment:										
Parameter	**All indications**		**ISA**		**SCLC**		**Patients excluded from ISA**		**Patients from IMforte**	
	Patients	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**
Creatinine clearance										
Normal (≥80 mL/min)	1,583	7,797.3	353	1,523.0	72	340.9	1,054	5,193.9	176	1,080.4
Mild (CrCl >60 to <80 mL/min)	358	1,970.1	124	656.2	21	113.0	185	1,031.8	49	282.1
Moderate (CrCl >30 to ≤60 mL/min)	190	972.2	76	324.8	11	46.5	100	538.6	14	108.7
Severe (CrCl ≤30 mL/min)	1	1.0	1	1.0	1	1.0	0	0	0	0
Missing	106	333.9	0	0	0	0	103	317.6	3	16.4
Creatinine										
≤ULN	2,002	9,939.7	474	2,184.6	88	441.1	1,304	6,391.2	224	1,363.9
>ULN and ≤1.5 ULN	182	878.9	75	313.2	16	59.3	92	460.0	15	105.6
>1.5 ULN and ≤3 ULN	21	79.1	5	7.2	1	1.0	13	53.8	3	18.1
>6 ULN	0	0	0	0	0	0	0	0	0	0
Missing	33	176.8	0	0	0	0	33	176.8	0	0
Total	**2,238**	**11,074.5**	**554**	**2,505.0**	**105**	**501.3**	**1,442**	**7,081.9**	**242**	**1,487.6**
Patients with cardiac impairment:**										
Parameter	**All indications**		**ISA**		**SCLC**		**Patients excluded from ISA**		**Patients from IMforte**	

	Patients	Person-months	Patients	Person-months	Patients	Person-months	Patients	Person-months	Patients	Person-months
LVEF ≥50	1,467	6,696.0	540	2,402.2	102	488.9	927	4,293.8	0	0
LVEF <50	12	32.5	3	13.5	0	0	9	19.0	0	0
Missing	759	4,346.0	11	89.3	3	12.4	506	2,769.1	242	1,487.6
Total	**2,238**	**11,074.5**	**554**	**2,505.0**	**105**	**501.3**	**1,442**	**7,081.9**	**242**	**1,487.6**
Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials					not included in the clinical development programme					
Population with relevant different ethnic origin.					Refer to section Part II: Module SIII - Clinical trial exposure					
Subpopulations carrying relevant genetic polymorphisms					not included in the clinical development programme					

* The data have been collected up to 29 July 2024, which has been defined as cut-off date
* Data from clinical trials JZP712-201, JZP712-101, PM1183-C-010-22 and PM1183-C-008-21 are not available and have not been included in this table
** Parameters data for cardiac impairment is not available in studies LY01017/CT-CHN-101, PM1183-A-007-13, PM1183-A-008-13, PM1183-A-013-15, PM1183-A-014-15 and PM1183-A-017-20
ISA, integrated safety analysis; SCLC, small cell lung cancer; ULN, upper limit of normal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Lurbinectedin was first approved in the US through an accelerated approval granted on 14 June 2020, under the tradename Zepzelca. To date, lurbinectedin has also been authorized in 17 countries including ten in Asia (United Arab Emirates, Singapore, South Korea, Qatar, Israel, Oman, Taiwan, Macau, China and Hong Kong); five in the Americas (US, Canada, Ecuador, Mexico, and Peru); one in Oceania (Australia) and one in Europe (Switzerland). Patients in the other European Countries currently can only benefit from lurbinectedin through compassionate use or in a clinical trial. The international birth date is 15 June 2020, based on the first approval.

SV. 1.1 Method used to calculate exposure

Estimated post-approval exposure from all sources (including commercial use) is summarized in this section.

Methodology

The market exposure for Zepzelca is estimated based on the data extracted from the sales information records received from the distributors; the sales volume is provided as the number of individual vials sold.

Historically, exposure was calculated considering launch assumptions of Zepzelca use in second line patients and third or later line patients of 34% and 66%, respectively. Those assumptions have evolved over time as more data became available and therefore, they have been adjusted to match the updated data:

- During the first year from the launch of the product (15 June 2020 to 30 June 2021), the patient use of Zepzelca was considered to be 53% in second line and 47% in third line. The estimated average of vials use per patient was 8 vials in second line and 6 in third line.
- For the period from 01 July 2021 until 30 June 2022, the patient use of Zepzelca was considered to be 62% in second line and 38% in third line. The estimated average of vials use per patient was 6.6 vials for both lines of treatment.
- For the period from 01 July 2022 until the cut-off date of this report, the patient use of Zepzelca was considered to be 64% in second line and 36% in third line use. The estimated average of vials use per patient was 6.6 vials for both lines of treatment.

Method limitations

The duration of the treatment itself may vary significantly based on the severity of the disease (e.g., patients who are severely ill might die before the recommended course of treatment).

SV. 1.2 Exposure

Table 17. Exposure table

Time period	Patient Type	No. of Vials*	Estimated use per patient	Estimated No. of Patients Exposed
0-1 Year from Launch 15Jun2020 / 30Jun2021	Second Line Patients (53%)	18,531	8 vials	2,316
	Third Line Patients (47%)	16,433	6 vials	2,739
1-2 Years from Launch 01Jul2021 / 30Jun2022	Second Line Patients (62%)	26,962	6.6 vials	4,085
	Third Line Patients (38%)	16,701	6.6 vials	2,530
2-3 Years from Launch 01Jul2022 / 29Jul2024	Second Line Patients (64%)	69,205	6.6 vials	10,486
	Third Line Patients (36%)	38,368	6.6 vials	5,814
Total (100%)		**186,200**		**27,970**

* Estimated number of vials distributed for patient use from 15 June 2020 to 29 July 2024

Cumulatively, the estimated number of vials distributed for patient use is approximately 186,200. The sales data are derived from the whole daily sales values cumulatively until 29 July 2024.

The estimated cumulative patient exposure through 29 July 2024 is 27,970 patients.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes.

Lurbinectedin must be administered under the supervision of a physician experienced in the use of chemotherapy, and its use should be confined to qualified oncologists or other health professionals specialised in the administration of cytotoxic agents. Therefore, no potential for misuse for illegal purposes is expected.

Part II: Module SVII - Identified and potential risks

Relevant information for the identification of important identified and important potential risks for lurbinectedin and any relevant updates on missing information are discussed below.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Myelosuppression

Reversible myelosuppression is the main toxicity for lurbinectedin. The most common haematological laboratory abnormality (all grades, regardless of relationship) is anaemia, with a frequency of 92.1% (510/554) in the ISA population and 94.3% (99/105) in the SCLC population. Neutropenia is the most common grade 3/4 haematological abnormality occurring in 40.8% (226/554) and 46.7% (49/105) of the ISA population and SCLC population, respectively. Grade 4 neutropenia was observed in 24.8% (26/105) of the SCLC population. Grade 3/4 thrombocytopenia was lower than 10% in both populations and not associated with bleeding.

Serious treatment emergent adverse events (TEAEs) of febrile neutropenia were reported in 6.1% (5.8% treatment related) and 4.8% (4.8% treatment related) of the ISA population and the SCLC population, respectively. All serious TEAEs of neutropenia/decreased ANC were assessed to be treatment related occurring with a frequency of 5.1% (ISA) and 5.7% (SCLC). Similarly, all serious TEAEs of thrombocytopenia/platelet count decreased were assessed to be related to treatment, occurring in 4.2% and 3.8% of the ISA and SCLC populations, respectively. Serious treatment related TEAEs of anaemia/ red blood cell decreased were reported in 2.5% of the ISA population and 3.8% of the SCLC population.

Infections in the presence of grade 3/4 neutropenia were observed in a similar percentage of patients (11.0% [61/554] and 8.6% [9/105]) in the ISA and SCLC populations, respectively; these were mostly respiratory disorders and the vast majority (91.9% and 92.9%) resolved. These infections had a median onset of 10 days after lurbinectedin administration and lasted a median of 6-7 days. Fatal outcome was reported in 3 patients in the ISA population (3/554: 0.5%), but not in patients in the SCLC population. Dose reduction was the most common action taken (2.7% and 5.7% of patients). Treatment discontinuation was required in 7 (1.3%) patients and one patient (1.0%) in the ISA and SCLC populations, respectively. G-CSFs were administered as secondary prophylaxis in 12 (2.2%) patients with infections and neutropenia in the ISA population, and in one patient (1.0%) in the SCLC population. Therapeutic G-CSFs were administered in 38 (6.9%) patients with infections and neutropenia in the ISA population, and in 5 (4.8%) patients in the SCLC population.

Preventative measures in the reference safety information for lurbinectedin include monitoring of full blood counts including differential white blood cells and platelet count at baseline and prior to each cycle and instructions to initiate treatment with lurbinectedin only if absolute neutrophil count is at least 1.5×10^9/L and platelet count is at least 100×10^9/L. The reference safety information also details criteria for making dose reductions and recommends the use of primary prophylaxis with G-CSF to reduce the risk of severe neutropenia/febrile neutropenia. Thus, the risk of myelosuppression is manageable and adequately reflected in the SmPC.

CPK elevations, including rhabdomyolysis

One case reporting CPK increased (in clinical study PM1183-A-002-10) and three cases reporting rhabdomyolysis (in clinical studies PM1183-A-002-10, PM1183-B-002-11 and PM1183-A-018-20) have been received. Two of the cases reporting rhabdomyolysis occurred with a higher dose of lurbinectedin (4.7 mg/m^2 and 3.4 mg/m^2 respectively). CPK elevations were reported in 7.8% of patients (1% grade 3/4) from the SCLC cohort of PM1183-B-005-14 versus 9.4% (0.4% grade 3/4) in the ISA population.

Based on the lurbinectedin mechanism of action, there is no direct link between the established primary pharmacodynamics of lurbinectedin, and the pathways known to cause rhabdomyolysis.

To further assess the potential risk of myositis and rhabdomyolysis, a global safety database analysis was conducted comparing patients from the integrated safety analysis (ISA) including the clinical trials PM1183-B-005-14 and PM1183-C-004-14 population (n=554; Group 1) with patients treated with lurbinectedin plus atezolizumab in the IMforte trial (n=242; Group 2). This analysis showed no statistically significant increase in the frequency or severity of rhabdomyolysis-related events in the combination therapy group compared with lurbinectedin monotherapy.

In addition, an external validation of the lurbinectedin reference population pharmacokinetics (popPK) model using pharmacokinetic data from the IMforte study showed that co-administration of lurbinectedin and atezolizumab is not expected to increase the exposure of either drug compared to the monotherapy administration, and thus not to raise the risk of rhabdomyolysis. Therefore, available data are not considered sufficient to support the inclusion of CPK elevations, including rhabdomyolysis as an important identified risk in the RMP.

However, preventive measures described in the reference safety information for lurbinectedin include dose modifications in the event of rhabdomyolysis, with recommendations to withhold treatment and/or permanently discontinue the medicinal product, as appropriate. Rhabdomyolysis is described as an adverse drug reaction for lurbinectedin and is also addressed under the Warnings and Precautions section of the SmPC. Specifically, if rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinization and dialysis should be promptly established, as indicated. Caution should be taken if medicinal products with known association with rhabdomyolysis (e.g. statins), are administered concomitantly with lurbinectedin, since the risk of rhabdomyolysis may be increased.

Overall, the risk of rhabdomyolysis is considered manageable and adequately addressed in the SmPC.

Gastrointestinal Disorders

Gastrointestinal TEAEs were common in both the ISA population and SCLC population with the following frequencies: constipation (32.3% and 32.4%), diarrhoea (19.0% and 20.0%), nausea (57.2% and 38.1%), vomiting (30.3% and 21.9%) and decreased appetite (25.1% and 34.3%). Treatment-related gastrointestinal TEAEs were reported with the following frequencies: constipation (16.8% and 9.5%), diarrhoea (12.8% and 13.3%), nausea (50.9% and 33.3%), and vomiting (25.1% and 18.1%) and decreased appetite (17.1% and 21.9%).

Although gastrointestinal TEAEs were common, these are not considered important for inclusion in the list of safety concerns in the RMP because those events were mostly mild to moderate without any associated complication.

Fatigue

Fatigue was reported as a TEAE in 63.2% and 77.1% of the ISA population and SCLC population, respectively. The corresponding frequencies for treatment related TEAEs for fatigue were 52.5% in the ISA Population and 59% in the SCLC population.

Although fatigue TEAEs were common, these are not considered important for inclusion in the list of safety concerns in the RMP because those events were mostly mild to moderate without any associated complication.

Liver enzymes increase

Increases in ALT (all grades, regardless of relationship) were observed in 65.6% (361/550) of the ISA population and 71.8% (74/103) of the SCLC population. Grade ≥3 ALT increases were reported in a low number 6.4% (35/550) and 3.9% (4/103) in the ISA population and SCLC population, respectively. These ALT increases had a median onset on Day 8, median peak value of 6.2-6.4× ULN, and median duration of 7 days. Increases in AST (all grades, regardless of relationship) were observed in 52.7% (290/550) of the ISA population and 44.7% (46/103) of the SCLC population. Grade ≥3 AST increases were reported in a low number 3.3% (18/550) and 1.9% (2/103) in the ISA population and SCLC population, respectively. The potential for lurbinectedin to cause severe liver injury, as defined in the FDA's Guidance for Industry: Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation, was evaluated in the ISA population (17). No Hy's Law cases as defined in the aforementioned FDA's Guidance for Industry were found among the 554 patients treated with lurbinectedin in this population.

Liver enzymes increase TEAEs are not considered important for inclusion in the list of safety concerns in the RMP because those events are adequately addressed in the reference safety information in which advice is given on monitoring of liver test including ALT, AST and bilirubin prior to initiating lurbinectedin and periodically during treatment as clinically indicated. It also advises to withhold the dose of lurbinectedin in the event of grade 2 hepatotoxicity until grade ⩽1 (for AST and ALT until ⩽ 3 ULN) and resume at the same dose. In case of grade ⩾3 (severe) hepatotoxicity lurbinectedin should be withhold until the grade ⩽1 (for AST and ALT until ⩽ 3 ULN) and resume at reduced dose. The benefit of treatment with lurbinectedin in SCLC patients outweighs the risk of transient increases in liver enzymes which can be minimised with the preventative measures in place.

Injection site reaction, including extravasation

A low percentage of patients (26/554: 4.7% in the ISA population and 7/105: 6.7% in the PM1183-B-005-14 SCLC population) had this type of events, all of them being grade 1 or 2. Among others, these events comprised injection site or infusion site phlebitis (five patients [5/554: 0.9%] in the ISA population and one [1/105: 1.0%] in the PM1183-B-005-14 SCLC population) and infusion site extravasations or extravasations (three patients [3/554: 0.5%] in the ISA population and one [1/105: 1.0%] in the PM1183-B-005-14 SCLC population). Only one patient treated in study PM1183-C-004-14 (1/554: 0.2%) required lurbinectedin treatment discontinuation because of both grade 2 infusion site extravasation and grade 1 catheter site related reaction (18). An undesirable complication related to the administration of antineoplastic therapy is injection site reaction potentially leading to extravasation of chemotherapy especially if the solution given is viscous and administered in a non-filtered manner.

Injection site reaction, including extravasation TEAEs are not considered important for inclusion in the list of safety concerns in the RMP because those events are adequately addressed in the reference safety

information for the product that recommends the use of a central venous catheter to reduce the risk of extravasation and thrombophlebitis, particularly in patients with limited venous access and to monitor patients for signs and symptoms of extravasation during lurbinectedin infusion. If extravasation occurs, the infusion should be immediately discontinued, the infusion catheter should be removed, and patient should be monitored for signs and symptoms of tissue necrosis. The time to onset of necrosis after extravasation may vary.

Supportive care should be administered and an appropriate medical specialist should be consulted as needed for management of signs and symptoms of extravasation. Subsequent infusions should be administered at a site that was not affected by extravasation.

Acute myeloid leukaemia/ Myelodysplasia

Based on its mechanism of action, lurbinectedin is a DNA-binding, genotoxic compound and therefore has a theoretical potential to increase the risk of tumourigenic effects, including the development of secondary malignancies such as acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS). However, therapy-related AML/MDS is typically associated with prolonged and/or high cumulative exposure to genotoxic agents.

No cases of AML or MDS were reported in the SCLC cohort of study PM1183-B-005-14. One case of MDS was reported in the ISA population in study PM1183-C-004-14. This event occurred in a 77-year-old Caucasian female who developed MDS approximately two months and three weeks after the last dose of lurbinectedin. Although the patient received 33 cycles of lurbinectedin at a dose of 3.2 mg/m², the most plausible contributors to the development of therapy-related MDS were the long-term cumulative exposure to carboplatin (approximately 5 years and 3 months) and to an anthracycline (pegylated liposomal doxorubicin; approximately 3 years and 3 months), both of which are well-established risk factors for secondary MDS.

Additionally, one case of AML was reported in the GO43104/IMforte clinical trial in a 64-year-old male patient, with onset approximately three months and one week after the last dose of lurbinectedin. The patient had received 15 cycles of lurbinectedin. Among the multiple prior and concomitant anticancer treatments administered (including etoposide, carboplatin, lurbinectedin, atezolizumab, and radiotherapy), etoposide was considered the agent most strongly associated with the development of AML, given its classification as a topoisomerase II inhibitor and the well-documented causal association of this drug class with therapy-related AML.

In both cases, alternative anticancer therapies with a recognized leukemogenic potential (i.e., etoposide and anthracyclines) were identified as the most likely contributors to the occurrence of AML/MDS.

Based on the available clinical data, AML/MDS is not considered an important identified or potential risk warranting inclusion in the RMP. This conclusion is supported by the relatively short median duration of exposure to lurbinectedin in the claimed indication (typically <6 months), which is not consistent with the prolonged cumulative exposure generally associated with therapy-related AML/MDS.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Potential Risk: Embryo-foetal toxicity

Risk-benefit impact:

Carcinogenicity testing of lurbinectedin has not been performed. In pre-clinical studies, lurbinectedin induced maternal toxicity at the single dose MTD level of 0.6 mg/m^2 administered on Day 10 post-*coitum* and severe embryo-toxicity, leading to 100% embryo lethality. Lurbinectedin is known to be

genotoxic to mammalian cells. It was mutagenic in the mouse lymphoma cell assay. Lurbinectedin was not mutagenic *in vitro* in a bacterial reverse mutation (Ames) assay.

Preventative measures in the reference safety information include advising of the potential foetal harm of lurbinectedin when administered to a pregnant woman. Pregnancy testing is recommended in women of childbearing potential prior to starting treatment. Female patients of childbearing potential are advised to use highly effective contraception during treatment and for 7 months after the last dose.

Male patients with female partners of childbearing potential are advised to use condom during treatment and for 4 months after the last dose. Female partners of childbearing potential should use highly effective contraception for the same period.

These measures, if adhered to, should minimise the risk of foetal harm.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

This section is not applicable as this is an initial marketing authorisation application.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Potential Risk: Embryo-foetal toxicity *(MedDRA System Organ Class [SOC] Congenital, familial and genetic disorders or SOC Pregnancy, puerperium and perinatal conditions or cases with a classification of Pregnancy Exposure/Pregnancy or cases with a classification of Parent/Child or cases in which the patient age group is "neonate" or "infant" or cases in which the patient is a child aged ⩽3 years old).*

Potential mechanisms:

The nature of lurbinectedin (cytotoxic and mutagenic) suggests that it is likely to affect the reproductive capacity.

Evidence source(s) and strength of evidence:

There are no available data with the use of lurbinectedin during human pregnancy. Animal studies in pregnant rats during the period of organogenesis demonstrated embryo-foetal lethality and maternal toxicity. Based on its mechanism of action, lurbinectedin may cause foetal harm when administered during pregnancy.

Characterisation of the risk:

Details of the frequency, severity and outcome of the TEAEs relating to Embryo-foetal toxicity are summarised for lurbinectedin monotherapy for the ISA (PM1183-B-005-14, PM1183-C-004-14) population in Table 18. A similar summary is provided in Table 19 for all studies excluding the ISA (PM1183-B-005-14, PM1183-C-004-14) population, PM1183-C-003-14 and 15 crossover patients from PM1183-B-002-11. No TEAEs were reported for SCLC patients concerning the risk of Embryo-foetal toxicity.

Table 18. Summary of TEAEs concerning the risk of Embryo-foetal toxicity for ISA (PM1183-B-005-14, PM1183-C-004-14) population*

	Lurbinectedin (n=554)
Any Event regardless of relationship, n (%)	1 (0.2%)
Severity based on AEs (Grade 1), n (%)	1 (0.2%)

* The data presented collected up to 29 July 2024, which has been defined as cut-off date

Table 19. Summary of TEAEs concerning the risk of Embryo-foetal toxicity for all studies excluding ISA (PM1183-B-005-14, PM1183-C-004-14) population, PM1183-C-003-14 and 15 crossover patients from PM1183-B-002-11*

	Lurbinectedin (n=1,123)
Any Event regardless of relationship, n (%)	1 (0.1%)
Outcome based on SAEs (Resolved), n (%)	1 (0.1%)
Severity based on AEs (Grade 3), n (%)	1 (0.1%)

* The data presented collected up to 29 July 2024, which has been defined as cut-off date
* Data from clinical trials PM1183-C-008-21, PM1183-C-010-22, JZP712-201: EMERGE-201 and JZP712-101: EMERGE-101 are not available and have not been included in this table

No TEAEs were reported for the 219 patients receiving lurbinectedin and the 213 patients in the positive control arm (PLD or topotecan) in study PM1183-C-004-14 (platinum-resistant ovarian cancer).

Details of the frequency, severity and outcome of the TEAEs relating to Embryo-foetal toxicity for the 242 patients receiving the combination of lurbinectedin with atezolizumab and the 240 patients in the control arm (atezolizumab) in study IMforte (GO43104) are summarised in Table 20.

Table 20. Summary of TEAEs concerning the risk of Embryo-foetal toxicity for IMforte (GO43104)*

	Group A: Lurbinectedin+Atezolizumab (n=242)	Control Arm B: Atezolizumab (n=240)	Odds Ratio (95% CI)
Any Event regardless of relationship, n (%)	1 (0.4%)	1 (0.4%)	0.99 (0.06-15.95)
Severity based on AEs (Grade 1), n (%)	1 (0.4%)	1 (0.4%)	

* The data presented collected up to 29 July 2024, which has been defined as cut-off date

No TEAEs were reported concerning the risk of Embryo-foetal toxicity for the 303 patients receiving lurbinectedin and doxorubicin and the 289 patients in the positive control arm (CAV or topotecan) in study PM1183-C-003-14.

Risk factors and risk groups:

Pregnant and non-pregnant women of childbearing potential.

Preventability:

Preventative measures in the reference safety information include advising female patients of childbearing potential to use highly effective contraception during treatment and for 7 months after the last dose. Pregnancy testing is recommended in women of childbearing potential prior to starting treatment. Male patients with female partners of childbearing potential should use condom during treatment and for 4 months after the last dose. Female partners of childbearing potential should use highly effective contraception for the same period.

Impact on the risk-benefit balance of the product:

The impact on the risk-benefit balance of the product is expected to be low, as preventative measures, if adhered to, should minimise the risk of foetal harm.

Public health impact:

The public health impact of these events is expected to be low, as their incidence is very low.

SVII.3.2 Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table 21. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include closely monitoring of case reports from both clinical trial and post-marketing settings, focusing on the collection, evaluation of the risk factors, severity, seriousness, and outcome but also the reporting to applicable competent authorities. Furthermore, ongoing evaluation of aggregate safety information from all sources from interval periods and cumulative will be performed, including trending analysis for all safety concerns in the Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report (PSUR/PBRER).

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction Follow-up Questionnaires are in place for:

None.

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are being conducted.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No planned or on-going imposed post-authorisation efficacy studies are in place for lurbinectedin.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 22. Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Embryo-foetal toxicity	**Routine risk communication:** *SmPC Section 4.4 Special warnings and precautions for use* *SmPC Section 4.6 Fertility, pregnancy and lactation* *SmPC Section 5.3 Preclinical safety data* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC Section 4.4 Special warnings and precautions for use* *Embryo-foetal toxicity* Lurbinectedin can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended in women of childbearing potential prior to starting treatment.

Safety concern	Routine risk minimisation activities
	Female patients of childbearing potential should use highly effective contraception during treatment with lurbinectedin and for 7 months after the last dose. Male patients with female partners of childbearing potential should use condom during treatment and for 4 months after the last dose. Female partners of childbearing potential should use highly effective contraception for the same period. *SmPC Section 4.6 Fertility, pregnancy and lactation* Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with lurbinectedin. Female patients of childbearing potential should use highly effective contraception during treatment and for 7 months after the last dose. Male patients with female partners of childbearing potential should use condom during treatment and for 4 months after the last dose. Female partners of childbearing potential should use highly effective contraception for the same period. *Pregnancy* There are no or limited amount of data from the use of lurbinectedin in pregnant women. Studies in animals have shown severe embryo-foetal development toxicity. Lurbinectedin should not be used during pregnancy unless the clinical condition of the woman requires treatment with lurbinectedin. Pregnant or non-pregnant women of childbearing potential should be advised of the potential risk to a foetus. If lurbinectedin is used during pregnancy, or if a patient becomes pregnant while receiving lurbinectedin, the patient should be apprised of the potential risk to the foetus. *Breast-feeding* It is unknown whether lurbinectedin/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Lurbinectedin is contraindicated during breastfeeding. *Fertility* Although no specific studies were conducted to assess fertility with lurbinectedin, and no clear signals of toxicity of reproductive organs were observed in toxicity studies, due to the nature of the compound (cytotoxic and mutagenic) it is likely to affect the reproductive capacity. Advice on conservation of ovules or sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with lurbinectedin. Genetic counselling is also recommended for patients wishing to have children after therapy.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 23. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Embryo-foetal toxicity	**Routine risk minimisation measures:** *SmPC Section 4.4 Special warnings and precautions for use Embryo-foetal toxicity* Pregnancy testing is recommended in women of childbearing potential prior to starting treatment. Advice is given to female patients of childbearing potential to use highly effective contraception during treatment and for 7 months after the last dose. Male patients with female partners of childbearing potential are advised to use condom during treatment and for 4 months after the last dose. For female partners of childbearing	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	potential highly effective contraception is also advised for the same period. *SmPC Section 4.6 Fertility, pregnancy and lactation* Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with lurbinectedin. Female patients of childbearing potential are advised to use highly effective contraception during treatment and for 7 months after the last dose. Male patients with female partners of childbearing potential are advised to use condom during treatment and for 4 months after the last dose. For female partners of childbearing potential highly effective contraception is also advised for the same period. *Pregnancy* Lurbinectedin should not be used during pregnancy unless the clinical condition of the woman requires treatment with lurbinectedin. Pregnant or non-pregnant women of childbearing potential should be advised of the potential risk to a foetus. If lurbinectedin is used during pregnancy, or if a patient becomes pregnant while receiving lurbinectedin, the patient should be apprised of the potential risk to the foetus. *Breast-feeding* Lurbinectedin is contraindicated during breastfeeding. *Fertility* Advice on conservation of ovules or sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with lurbinectedin. Genetic counselling is also recommended for patients wishing to have children after therapy. **Additional risk minimisation measures:** None.	

Part VI: Summary of the risk management plan

Summary of risk management plan for Zepzelca (lurbinectedin)

This is a summary of the risk management plan (RMP) for Zepzelca. The RMP details important risks of Zepzelca, how these risks can be minimised, and how more information will be obtained about Zepzelca's risks and uncertainties (missing information).

Zepzelca's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zepzelca should be used.

This summary of the RMP for Zepzelca should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zepzelca's RMP.

I. The medicine and what it is used for

Zepzelca in combination with atezolizumab is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide (see SmPC for the full indication). It contains lurbinectedin as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Zepzelca's benefits can be found in Zepzelca's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of lurbinectedin, together with measures to minimise such risks and the proposed studies for learning more about lurbinectedin's risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Updated Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of lurbinectedin is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Zepzelca are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of lurbinectedin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	None

II.B Summary of important risks

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	There are no available data with the use of lurbinectedin during human pregnancy. Animal studies in pregnant rats during the period of organogenesis demonstrated embryo-foetal lethality and maternal toxicity. Based on its mechanism of action, lurbinectedin may cause foetal harm when administered during pregnancy.
Risk factors and risk groups	Pregnant and non-pregnant women of childbearing potential.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC Section 4.4 Special warnings and precautions for use* *Embryo-foetal toxicity*

	Pregnancy testing is recommended in women of childbearing potential prior to starting treatment. Advice is given to female patients of childbearing potential to use highly effective contraception during treatment and for 7 months after the last dose. Male patients with female partners of childbearing potential are advised to use condom during treatment and for 4 months after the last dose. For female partners of childbearing potential highly effective contraception is also advised for the same period. *SmPC Section 4.6 Fertility, pregnancy and lactation* Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with lurbinectedin. Female patients of childbearing potential are advised to use highly effective contraception during treatment and for 7 months after the last dose. Male patients with female partners of childbearing potential are advised to use condom during treatment and for 4 months after the last dose. For female partners of childbearing potential highly effective contraception is also advised for the same period. *Pregnancy* Lurbinectedin should not be used during pregnancy unless the clinical condition of the woman requires treatment with lurbinectedin. Pregnant or non-pregnant women of childbearing potential should be advised of the potential risk to a foetus. If lurbinectedin is used during pregnancy, or if a patient becomes pregnant while receiving lurbinectedin, the patient should be apprised of the potential risk to the foetus. *Breast-feeding* Lurbinectedin is contraindicated during breastfeeding. *Fertility* Advice on conservation of ovules or sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with lurbinectedin. Genetic counselling is also recommended for patients wishing to have children after therapy. **Additional risk minimisation measures:** None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of lurbinectedin.

II.C.2 Other studies in post-authorisation development plan

There are no studies in post-authorisation development plan.

Part VII: Annexes

Table of contents

Annex Tables

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7: Other supporting data (including referenced material)

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