PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrZEPZELCA®

lurbinectedin for injection

Lyophilized powder, 4 mg / vial, intravenous infusion

Antineoplastic Agent

"ZEPZELCA, indicated for:

- the treatment of adult patients with Stage III or metastatic small cell lung cancer (SCLC) who have progressed on or after platinum-containing therapy

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ZEPZELCA please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html"

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

3 Serious Warnings and Precautions Box	06/2022
4 Dosage and Administration, 4.1 Recommended Dose and Dosage Adjustment	12/2022
4 Dosage and Administration, 4.3 Administration	06/2022
7 Warnings and Precautions	12/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

NOC/c 1 INDICATIONS

ZEPZELCA (lurbinectedin) is indicated for:

- treatment of adult patients with Stage III or metastatic small cell lung cancer (SCLC) who have progressed on or after platinum-containing therapy.

The marketing authorization with conditions was based on overall response rate and duration of response; no overall survival benefit has been demonstrated (see **14** **CLINICAL TRIALS**).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): No overall difference in effectiveness was observed between SCLC patients aged 65 and older (35% of study population) and younger patients. However, there was a higher incidence of serious adverse reactions in patients ≥ 65 years of age than in patients < 65 years of age (49% vs. 26%, respectively) (see **7** **WARNINGS AND PRECAUTIONS – Special Populations**).

NOC/c 2 CONTRAINDICATIONS

- ZEPZELCA is contraindicated in patients who are hypersensitive to this drug or to any drug ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6** **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

NOC/c 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

ZEPZELCA should be administered under the supervision of a physician who is experienced in the use of cancer chemotherapeutics.

Consider use of a central venous catheter to reduce the risk of extravasation with ZEPZELCA (see **7** **WARNINGS AND PRECAUTIONS** - Injection Site Reactions and **4** **DOSAGE AND ADMINISTRATION** sections below).

The following are clinically significant adverse events:

- Myelosuppression, including fatal cases (see **7** **WARNINGS AND PRECAUTIONS – Hematologic**).
- Embryofetal toxicity (see **7** **WARNINGS AND PRECAUTIONS** **and** **Non-clinical toxicology**).
- Injection site reactions (see **7** **WARNINGS AND PRECAUTIONS** - **Injection Site Reactions** section below).

NOC/c 4 DOSAGE AND ADMINISTRATION

Administer ZEPZELCA only if:

- Neutrophil count is at least 1,500 cells/mm^3 (1.5 x 10^9/L).
- Platelet count is at least 100,000/mm^3 (100 x 10^9/L).
- Hemoglobin count is at least 90 g/L upon initiation of treatment or at least 80 g/L for subsequent treatment cycles. If clinically indicated, patients may receive red blood cell (RBC) transfusions to increase or maintain adequate hemoglobin levels.
- Albumin levels are at least 30 g/L.
- Patients with grade 4 neutropenia (neutrophil counts less than 500 cells/mm^3 (0.5 x 10^9/L)) or with any value less than the lower limit of normal that is associated with infection/sepsis may receive G-CSF rather than undergo a dose reduction.
- Routine pre-infusion and post-infusion administration of the following antiemetic prophylaxis is recommended:
    - Corticosteroids (i.e. dexamethasone 8 mg intravenously or equivalent).
    - Serotonin antagonists (i.e. ondansetron 8 mg intravenously or equivalent).

4.1 Recommended Dose and Dosage Adjustment

The recommended dose is 3.2 mg/m^2 by intravenous infusion over 60 minutes repeated every 21 days until disease progression or unacceptable toxicity.

Permanently discontinue ZEPZELCA in patients who are unable to tolerate 2 mg/m^2 or require a dose interruption greater than two weeks.

Dose reductions

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

Table 1. ZEPZELCA Dose Reduction Schedule

Recommended Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
3.2 mg/m^2 every 21 days	2.6 mg/m^2 every 21 days	2.0 mg/m^2 every 21 days	Stop

Dose modifications

The recommended dose modifications for adverse reactions are listed in Table 2.

Table 2. Dosage Modifications Criteria for ZEPZELCA for Specific Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification
Neutropenia	Grade 4 or Any grade febrile neutropenia	Withhold ZEPZELCA until Grade ≤1 *and* Resume ZEPZELCA at a reduced dose
Thrombocytopenia	Grade 3 with bleeding or Grade 4	Withhold ZEPZELCA until platelet ≥100 x 10^9/L *and* Resume ZEPZELCA at reduced dose
Hepatotoxicity and other adverse reactions	Grade 2	Withhold ZEPZELCA until Grade ≤1 *and* Resume ZEPZELCA at same dose
	Grade ≥3	Withhold ZEPZELCA until Grade ≤1 *and* Resume ZEPZELCA at reduced dose
Rhabdomyolysis	Grade 2	Withhold ZEPZELCA until Grade ≤1 *and* Resume ZEPZELCA at same dose
	Grade ≥3	Permanently discontinue ZEPZELCA
Neutropenia associated with infection/sepsis	Any grade	Reduce the dose of ZEPZELCA

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0

Special Populations

Renal insufficiency

No dose adjustment is required in patients with mild (CrCl 60-89 mL/min) or moderate (CrCl of 30-59 mL/min) renal impairment (see **10 CLINICAL PHARMACOLOGY**).

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

Hepatic insufficiency

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

moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST) (see **10 CLINICAL PHARMACOLOGY**).

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

Pediatric patients

Health Canada has not authorized an indication for pediatric use (see **1 INDICATIONS**).

4.2 Reconstitution

Parenteral Products:

- ZEPZELCA is a cytotoxic drug. Follow applicable special handling and disposal procedures.
- Prepare the solution for infusion using aseptic technique as follows:
  - Inject 8 mL of Sterile Water for Injection USP into the vial. Shake the vial until complete dissolution. The reconstituted solution is a clear, colourless or slightly yellowish solution, essentially free of visible particles.
  - Visually inspect the solution for particulate matter and discoloration. If particulate matter or discoloration is observed, do not administer. Dilute the reconstituted solution with 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP.
  - Calculate the required volume of reconstituted solution as follows:

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

Table 3. Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
30 mL	8 mL	8.5 mL	0.5 mg/mL*

* The accurate (calculated) concentration is 0.47 mg/mL based on the final volume of 8.5 mL

4.3 Administration

Consider use of a central venous catheter to reduce the risk of extravasation with ZEPZELCA.

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

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

If infusion lines containing in-line filters are utilized for administration of ZEPZELCA, Polyethersulfone (PES) in-line filters with pore sizes of 0.22 micron are recommended.

Infusion lines containing Nylon membrane filters should not be used when the reconstituted ZEPZELCA solution is diluted with 0.9% Sodium Chloride Injection USP.

Compatibility with other IV administration materials and the diluted ZEPZELCA solution has been demonstrated in the following materials:

- Polyolefin containers (polyethylene, polypropylene and mixtures).
- PVC (non-DEHP-containing), polyurethane and polyolefin infusion sets (polyethylene, polypropylene and polybutadiene).
- Implantable venous access systems with titanium and plastic resin ports and with polyurethane or silicone intravenous catheters.

Do not co-administer ZEPZELCA and other intravenous drugs concurrently within the same intravenous line.

If not used immediately after reconstitution or dilution, the diluted solution can be stored prior to administration for up to 24 hours following reconstitution, including infusion time, at either room temperature/ambient light or under refrigerated (2°C to 8°C) conditions.

5 OVERDOSAGE

If an overdose is suspected, monitor the patient closely for myelosuppression and abnormal hepatic function (elevated hepatic enzymes), and institute supportive-care measures as appropriate.

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

There is no known antidote for overdosage with ZEPZELCA.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous (IV) infusion	Lyophilized powder/ 4 mg per vial	lactic acid, sodium hydroxide, sucrose

ZEPZELCA is a sterile, white to off-white, preservative free lyophilized powder contained within a colourless type I glass vial, with rubber stopper and aluminum seal containing 4 mg of lurbinectedin. ZEPZELCA is provided in cartons containing one single-dose vial.

NOC/c 7 WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

Carcinogenicity testing of ZEPZELCA has not been performed. ZEPZELCA is genotoxic to mammalian cells in the presence and absence of metabolic activation (See **16** **NON-CLINICAL TOXICOLOGY**).

Driving and Operating Machinery

No studies on the effects of the ability to drive and to use machines have been performed. However,

some events of fatigue have been reported in patients receiving lurbinectedin. Patients who experience such events during therapy should not drive or operate machinery.

Hematologic

ZEPZELCA causes myelosuppression.

From pooled data of 554 patients receiving ZEPZELCA, as a single agent every 21 days, which included patients with SCLC and other solid tumours, all grade neutropenia occurred in 64% of patients. Grade 3/4 neutropenia occurred in 41% of patients with a median onset at Day 15 and a duration of 7 days. Neutropenia led to dose reduction in 11% of patients and to treatment discontinuation in one patient. Febrile neutropenia occurred in 7% of patients. Sepsis occurred in 2% of patients and was fatal in 1% (all 3 cases occurred in patients with solid tumours other than SCLC). All grade thrombocytopenia was experienced by 49% of patient. Grade 3 or 4 thrombocytopenia occurred in 10%, with a median time to onset of 10 days and a median duration of 7 days. Thrombocytopenia led to dose reduction in 3% and to treatment discontinuation in 2 patients. All grade anemia occurred in 92% of patients and grade 3 or 4 anemia occurred in 17% of patients. Anemia resulted in dose reduction in 1 patient and treatment discontinuation in 2 patients.

Administer ZEPZELCA only to patients with baseline neutrophil count of at least 1,500 cells/mm^3 (1.5 x 10^9/L) and platelet count of at least 100,000/mm^3 (100 x 10^9/L). In case of neutrophil counts of less than 500 cells/mm^3 (0.5 x 10^9/L) or any value less than lower limit of normal, the use of G-CSF is recommended. Obtain complete blood cell counts prior to initiation of therapy and prior to each treatment cycle. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity (see **7 WARNINGS & PRECAUTIONS -Monitoring and Laboratory Tests**).

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Among the 554 patients treated with ZEPZELCA at the recommended dose and schedule, all grade ALT increases were observed in 66% of patients and these were grade 3/4 in severity in 6% of patients. All grade AST elevations occurred in 53% of patients and these were grade 3/4 in severity in 3% of patients. The median time to onset of Grade ≥3 elevation in transaminases was 8 days (range: 3 to 49), with a median duration of 7 days.

ZEPZELCA has not been studied in patients with moderate or severe hepatic impairment. Patients with AST >3 x ULN and/or bilirubin >1.5 X ULN were not allowed to participate in clinical trials of ZEPZELCA.

Injection Site Reactions

Extravasation of ZEPZELCA resulting in skin and soft tissue injury, including necrosis requiring debridement, can occur. Consider use of a central venous catheter to reduce the risk of extravasation, particularly in patients with limited venous access.

Monitor patients for signs and symptoms of extravasation during the ZEPZELCA infusion. If extravasation occurs, immediately discontinue the infusion, remove the infusion catheter, and monitor for signs and symptoms of tissue necrosis. The time to onset of necrosis after extravasation may vary.

Administer supportive care and consult with an appropriate medical specialist as needed for signs and symptoms of extravasation. Administer subsequent infusions at a site that was not affected by extravasation (See section **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**).

Monitoring and Laboratory Tests

Obtain complete blood counts prior to initiation of therapy and prior to each cycle. Patients should have albumin levels at least 30 g/L prior to administration of ZEPZELCA. (see **4** **DOSAGE AND ADMINISTRATION**).

Monitor liver function tests prior to initiating ZEPZELCA, periodically during treatment and as clinically indicated. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity of the adverse events (See **4** **DOSAGE AND ADMINISTRATION – Dose Modifications**).

Monitor for signs and symptoms of peripheral neuropathy after the initiation of ZEPZELCA. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity of the adverse events (See **4** **DOSAGE AND ADMINISTRATION – Dose Modifications**).

Monitor for signs and symptoms of rhabdomyolysis through plasma creatine kinase (CK), or urinary myoglobin levels prior to initiating ZEPZELCA and periodically during treatment as clinically indicated. Withhold or reduce the dose based on severity (See **4** **DOSAGE AND ADMINISTRATION – Dose Modifications**).

Musculoskeletal

Rhabdomyolysis has been reported in patients treated with ZEPZELCA.

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(see **7** **WARNINGS & PRECAUTIONS - Monitoring and Laboratory Tests**).

Neurologic

Among the 554 patients treated with ZEPZELCA at the recommended dose and schedule, all grade peripheral neuropathy (which includes the additional events of paraesthesia, peripheral sensory neuropathy, hypoaesthesia, dysaesthesia, hyperaesthesia, peripheral motor neuropathy, and polyneuropathy) occurred in 9 of patients. Grade 3/4 peripheral neuropathy occurred in 2 patients. Peripheral neuropathy led to dose reduction in 2 patients and to treatment discontinuation in 1% of patients.

Reproductive Health: Female and Male Potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving ZEPZELCA.

Advise female patients of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 6 months after the last dose. Advise pregnant women of the potential risk to the fetus.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 4 months after the last dose.

- **Fertility**

  Fertility studies with lurbinectedin were not performed. There were no clear findings in reproductive organs in general toxicology studies in rats, dogs, or monkeys; however, the highest doses and exposures in these studies were all at levels lower than the human dose of 3.2 mg/m^2.

- **Teratogenic Risk**

  Based on animal data and its documented mechanism of action (leading to double strand breaks and cell death), ZEPZELCA can cause fetal harm when administered to a pregnant woman. Animal studies in pregnant rats during the period of organogenesis reported embryo-fetal lethality and maternal toxicity following administration of a single intravenous dose of 0.6 mg/m^2 ZEPZELCA (approximately equivalent to 20% of the estimated human dose of 3.2 mg/m^2) (See **16 NON-CLINICAL TOXICOLOGY).**

7.1 Special Populations

7.1.1 Pregnant Women

ZEPZELCA should not be used during pregnancy.

There are no available data to inform on the risk of using ZEPZELCA during human pregnancy. Animal studies in pregnant rats during the period of organogenesis reported embryo-fetal lethality and maternal toxicity following administration of a single dose of 0.6 mg/m^2 ZEPZELCA (approximately equivalent to 20% of the estimated human dose of 3.2 mg/m^2). Lurbinectedin was also genotoxic *in vitro* in mammalian cell lines.

If this drug is used during pregnancy, or if a patient could become pregnant while receiving ZEPZELCA, the patient should be informed of the potential risk to the fetus.

7.1.2 Breast-feeding

There are no data on the presence of lurbinectedin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from ZEPZELCA in breastfed children, advise a nursing woman to discontinue nursing during treatment with ZEPZELCA and for 2 weeks after the final dose.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 105 patients with SCLC administered ZEPZELCA in clinical studies, 37 (35%) patients were 65 years of age and older, while 9 (9%) patients were 75 years of age and older. No overall difference in efficacy was observed between patients aged 65 and older and younger patients.

There was a higher incidence of grade ≥3 adverse events (76% vs. 50%) and of serious adverse events (49% vs. 27%) in patients ≥65 years of age than in patients <65 years of age. Grade ≥3 adverse events most frequently observed in patients ≥65 years of age were neutropenia (32% vs. 19%), fatigue (19% vs. 9%), anemia (11% vs. 7%), thrombocytopenia (11% vs. 0) and febrile neutropenia (11% vs. 2%).

The serious adverse events most frequently reported in patients ≥65 years of age consisted of febrile neutropenia (11% vs. 2%), neutropenia (11% vs. 2%), thrombocytopenia (8% vs. 0%), and anemia (8% vs. 2%).

Obtain complete blood cell counts prior to initiation of therapy and prior to each treatment cycle.

More frequent laboratory monitoring should be considered in patients who are >75 years of age, have poor performance status, have low blood albumin levels or are of low weight or have low body surface area.

Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity of the adverse events (see **4 DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment**).

NOC/c 8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Among the subset of patients with SCLC, the most common (≥20%) adverse reactions (all grades) were fatigue (77%), nausea (38%), decreased appetite (34%), musculoskeletal pain (34%), neutropenia (32%), constipation (32%), dyspnea (31%), vomiting (22%), respiratory tract infection (21%), diarrhea (20%) and cough (20%).

Grade ≥3 occurred in 59% of SCLC patients. The most frequent grade 3/4 reactions (occurring in ≥5 % of patients) were neutropenia (28%), fatigue (12%), anemia (9%), dyspnea (7%), pneumonia (7%), respiratory tract infection (5%), and thrombocytopenia (5%).

Serious adverse reactions occurred in 34% of patients who received ZEPZELCA. Serious adverse reactions in ≥2% of patients included respiratory tract infection (11%), neutropenia (5%), febrile neutropenia (5%), anemia (4%), dyspnea (4%), thrombocytopenia (3%) and musculoskeletal pain (2%).

Dose reductions due to an adverse reaction occurred in 27% of patients with SCLC who received ZEPZELCA. Adverse reactions requiring dose reduction in >2% of patients with SCLC who received ZEPZELCA included neutropenia (20%), febrile neutropenia (4%), fatigue (4%), thrombocytopenia (2%), and pneumonia (2%).

Dose interruptions due to an adverse reaction occurred in 48% of patients who received ZEPZELCA. Adverse reactions requiring dosage interruption in ≥3% of patients who received ZEPZELCA were neutropenia (14%) and hypoalbuminemia (5%).

Treatment discontinuation due to adverse reactions occurred in 2% of patients with SCLC who received ZEPZELCA and experienced peripheral neuropathy (n=1) and myelosuppression (n=1).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of ZEPZELCA was evaluated in a cohort of 105 patients with previously treated SCLC in Study B-005, a multicenter, single-arm phase 2 trial. Patients received ZEPZELCA 3.2 mg/m^2 intravenously every 21 days. The median age of the safety population was 60 years (range 40 to 83 years) with 35% of patients ≥ 65 years. A total of 60% of patients were male, 75% white, 23% other, 1% black or African American and 1% Asian. At enrollment, 36% patients had ECOG performance status (PS) of 0, 56% had PS of 1 and 8% had PS 2. The trial excluded patients with central nervous system (CNS) involvement, grade ≥3 dyspnea, daily intermittent oxygen requirement, hepatitis or cirrhosis, and immunocompromised patients. All patients in this study received a pre-specified anti-emetic regimen consisting of a corticosteroid and serotonin antagonist. Patients could receive G-CSF for secondary prophylaxis (i.e., after patients had an initial decrease in white blood cells), but not primary

prophylaxis. Among patients who received ZEPZELCA, median time on treatment was 14.3 weeks (range, 1.1-85.0 weeks) with 46% of patients receiving ≥6 cycles of treatment.

Table 5. Treatment-Emergent Adverse Events in ≥5% of SCLC Patients Who Received ZEPZELCA in Study B-005

System Organ Class Preferred Term[a]	SCLC (n=105)	
	All Grades[b] n (%)	Grade 3-4 n (%)
Gastrointestinal disorders		
Nausea	40 (38%)	-
Constipation	34 (32%)	-
Vomiting	23 (22%)	-
Diarrhea	21 (20%)	4 (4%)
Abdominal pain [c]	12 (11%)	1 (1%)
Stomatitis [d]	10 (10%)	-
Dysphagia	6 (6%)	1 (1%)
General disorders and administration site conditions		
Fatigue [e]	81 (77%)	13 (12%)
Pyrexia	14 (13%)	-
Chest pain	10 (10%)	-
Infections and infestations		
Pneumonia [f]	11 (11%)	7 (7%)
Respiratory tract infection [g]	22 (21%)	5 (5%)
Investigations		
Weight decreased	8 (8%)	1 (1%)
Metabolism and nutrition disorders		
Decreased appetite	36 (34%)	1 (1%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [h]	36 (34%)	4 (4%)
Nervous system disorders		
Neuropathy peripheral [i]	12 (11%)	-
Headache	10 (10%)	1 (1%)

System Organ Class Preferred Term[a]	SCLC (n=105)	
	All Grades[b] n (%)	Grade 3-4 n (%)
Dysgeusia	6 (6%)	-
Respiratory, thoracic and mediastinal disorders		
Dyspnea	32 (31%)	7(7%)
Cough	21 (20%)	-
Dysphonia	6 (6%)	-
Skin and subcutaneous tissue disorders		
Rash [j]	8 (8%)	-

[a] Reported adverse event terms were code using MedDRA v.21.0

[b] The severity of the TEAEs was graded based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4

[c] Merged together: abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain and epigastric discomfort

[d] Merged together: glossitis, mouth ulceration, aphthous ulcer, gingivitis and mucosal inflammation

[e] Merged together: asthenia

[f] Merged together: lung infection, atypical pneumonia and pneumocystis jirovecii pneumonia

[g] Merged together: bronchitis, upper respiratory tract infection, viral upper respiratory tract infection, and respiratory tract infection

[h] Merged together: back pain, pain in extremity, myalgia, musculoskeletal chest pain, neck pain and arthralgia

[i] Merged together: paraesthesia, peripheral sensory neuropathy, hypoaesthesia, dysaesthesia, hyperaesthesia, peripheral motor neuropathy and polyneuropathy

[j] Merged together: rash maculo-papular, urticaria, rash erythematous, rash papular, erythema, pruritus and pruritus generalized

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions have been observed in SCLC patients (<5%) who received ZEPZELCA.

Blood and lymphatic system disorders: Febrile neutropenia

General disorders and administration site conditions: Extravasation [a], Injection site reaction [b], Oedema peripheral [c], Pain

Musculoskeletal and connective tissue disorders: Muscle spasms, Muscular weakness

Nervous system disorders: Dizziness

Psychiatric disorders: Insomnia

Skin and subcutaneous tissue disorders: Alopecia, Dermatitis [d], Dermatitis exfoliative generalised

Vascular disorders: Superior vena cava syndrome

[a] Merged together: infusion site extravasation

[b] Merged together: catheter site pain, catheter site inflammation, catheter site related reaction, device related infection, catheter site infection, infusion related reaction, infusion site phlebitis, injection site erythema, injection site rash and injection site phlebitis

[c] Merged together: peripheral swelling

[d] Merged together: eczema, dermatitis bullous and dermatitis contact

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 6 summarizes the laboratory abnormalities experienced in more than 5% of the patients who received ZEPZELCA.

Table 6. Treatment-Emergent Laboratory Abnormalities Experienced by >5% of Patients in the SCLC patients who Received ZEPZELCA in Study B-005

Laboratory Abnormality[b]	SCLC patients (n=105)[a]	
	All Grades n (%)	Grades 3-4 n (%)
Hematological Abnormalities		
Anemia	99 (94%)	11 (11%)
Lymphopenia	90 (86%)	46 (44%)
Leukopenia	83 (79%)	30 (29%)
Neutropenia	75 (71%)	49 (47%)
Thrombocytopenia	46 (44%)	7 (7%)
Non-hematological Abnormalities		
Creatinine increased	86 (83%)	0%
Hyperglycemia	81 (79%)	5 (5%)
ALT increased	74 (72%)	4 (4%)
AST increased	46 (45%)	2 (2%)
Hyponatremia	42 (40%)	9 (9%)
Hypoalbuminemia	37 (37%)	1 (1%)
AP increased	34 (33%)	3 (3%)
Hyperkalemia	21 (20%)	0%
Hypokalemia	21 (20%)	1 (1%)
Hypercalcemia	16 (16%)	0%
Bilirubin increased	10 (10%)	0%
Hypocalcemia	9 (9%)	1 (1%)
CPK increased	8 (8%)	1 (1%)

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase

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

[b]The severity of the TEAEs was graded based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of ZEPZELCA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General and Administration Site Conditions: Extravasation including tissue necrosis requiring debridement.

Musculoskeletal and Connective Tissue Disorders: Cases of rhabdomyolysis

Endocrine and Metabolism: Cases of Tumour lysis syndrome

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

Dedicated clinical drug-drug interaction studies with CYP3A modulators have not been conducted with lurbinectedin.

In vitro Studies

Cytochrome P450 (CYP) Enzymes: Lurbinectedin is metabolized by CYP3A4. Lurbinectedin is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Lurbinectedin is not an inducer of CYP1A2 or CYP3A4.

Transporter Systems: Lurbinectedin is a substrate of MDR1, but is not a substrate of OATB1P1, OATP1B3, OCT1, or MATE1. Lurbinectedin inhibits MDR1, OATP1B1, OATP1B3, and OCT1 but not BCRP, BSEP, MATE1, OAT1, OAT3, or OCT2.

9.2 Drug-Drug Interactions

Strong and moderate CYP3A inhibitors

Coadministration with a strong or moderate CYP3A inhibitor increases lurbinectedin systemic exposure. Avoid coadministration of strong or moderate CYP3A inhibitors with ZEPZELCA. If coadministration with strong or moderate CYP3A inhibitors cannot be avoided, neutrophils and platelet counts should be carefully monitored, and possible dose modifications for adverse events may need to be considered (See **4 DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment**).

Strong and moderate CYP3A inducers

Coadministration with a strong CYP3A inducer decreases lurbinectedin systemic exposure which may reduce ZEPZELCA efficacy. Avoid coadministration of strong or moderate CYP3A inducers with ZEPZELCA. Consider alternative agents with less CYP3A induction.

9.3 Drug-Food Interactions

Grapefruit and Seville oranges or their juices are known to inhibit CYP3A and may increase lurbinectedin plasma concentration. Patients should avoid these fruits during ZEPZELCA treatment.

9.4 Drug-Herb Interactions

St. John's Wort (hypericum perforatum) is a strong CYP3A inducer. Co-administration with ZEPZELCA may lead to increased ZEPZELCA metabolism, therefore decreased ZEPZELCA serum concentration.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

NOC/c 10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lurbinectedin is an alkylating drug that inhibits the oncogenic transcription process through (i) its binding to cytosine-guanine (CG)-rich sequences of DNA, mainly located around promoters of protein-coding genes; (ii) the eviction of oncogenic transcription factors from their binding sites; and (iii) the stalling of elongating RNA polymerase II on those gene promoters and its specific degradation by the ubiquitin/proteasome machinery. These processes trigger a cascade of events that affect the activity of DNA binding proteins, including transcription factors, and DNA repair pathways leading to perturbation of the cell cycle and subsequent cellular apoptosis.

Lurbinectedin inhibits the transcription of selected cytokines by tumour-associated macrophages (TAMs) and reduces TAMs infiltration in human tumours implanted in mice, reducing their tumour-supportive roles.

10.2 Pharmacodynamics

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

Cardiac Electrophysiology

The potential for QTc prolongation with lurbinectedin was evaluated in 39 patients with advanced cancer. Large effects (>10 ms) on the QTc interval were not detected with lurbinectedin dosed at 3.2 mg/m^2 every 3 weeks.

10.3 Pharmacokinetics

After a 3.2 mg/m^2 lurbinectedin dose administered as a 1-hour intravenous infusion, geometric means of total plasma C_{max} and AUC∞, were 107 µg/L and 551 µg*h/L, respectively. No accumulation of lurbinectedin in plasma is observed upon repeated administrations every 3 weeks.

Table 7. Summary of lurbinectedin Pharmacokinetic Parameters in B-005 study; 3.2 mg/m^2 IV 1-h Infusion (n=329)

	C_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$	CL	Vd_{ss}
Single dose geometric mean	107 µg/L	51	551 µg*h/L	11 L/h	504 L

Distribution:

Typical volume of distribution of lurbinectedin at steady state is 504 L. Binding to plasma proteins is approximately 99%, to both albumin and α-1-acid glycoprotein.

Metabolism:

In vitro studies with human liver microsomes and supersomes indicate that CYP3A4 is the main CYP enzyme responsible for the hepatic metabolism of lurbinectedin.

Elimination:

The terminal half-life of lurbinectedin is 51 hours. Total plasma clearance of lurbinectedin is 11 L/h. The major route of lurbinectedin-related radioactivity excretion was via feces (89% of dose). The most abundant metabolite found in feces accounted for 1% of the dose and only traces of unchanged lurbinectedin were detected in feces (<0.2% of dose). Excretion in urine was the minor route (6% of dose), mainly as unchanged compound (1% of dose) and one metabolite (up to 1% of dose).

Special Populations and Conditions

Population pharmacokinetics analyses showed that weight (range: 39 to 154 kg), age (range: 18 to 85 years), and sex do not have a clinically meaningful influence of the systemic exposure of lurbinectedin.

- **Hepatic Insufficiency** 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 1.0-1.5 x ULN and any AST) who received ZEPZELCA 3.2 mg/m² every 3 weeks as compared to 625 patients with normal hepatic function.

  The pharmacokinetic characteristics of lurbinectedin in patients with moderate to severe hepatic impairment (total bilirubin >1.5 x ULN) are unknown.

- **Renal Insufficiency** Based on population pharmacokinetic analyses, no apparent pharmacokinetic difference was observed in 165 patients with mild renal impairment (CrCl of 60-89 mL/min), 73 patients with moderate renal impairment (CrCl of 30-59 mL/min), and one patient with severe renal impairment (CrCl of 26 mL/min) who received ZEPZELCA 3.2 mg/m² every 3 weeks as compared to 166 patients with normal renal function.

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

11 STORAGE, STABILITY AND DISPOSAL

Store unopened vial in refrigerator at 2°C to 8°C.

If not used immediately after reconstitution or dilution, the diluted solution can be stored prior to administration for up to 24 hours following reconstitution, including infusion time, at either room temperature/ambient light or under refrigerated (2°C to 8°C) conditions.

ZEPZELCA is a cytotoxic drug. Follow applicable disposal procedures.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

"ZEPZELCA, indicated for:

- the treatment of adult patients with Stage III or metastatic small cell lung cancer (SCLC) who have progressed on or after platinum-containing therapy

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ZEPZELCA please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html"

13 PHARMACEUTICAL INFORMATION

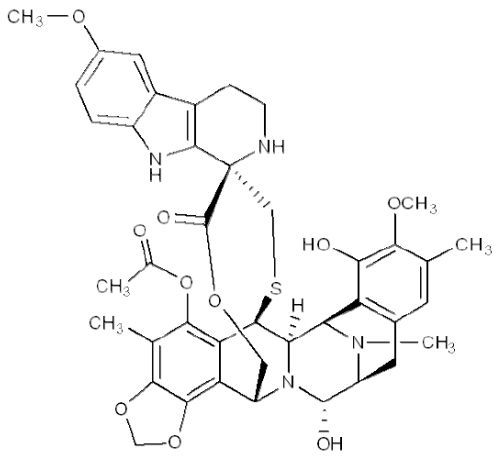
Drug Substance

Proper name: lurbinectedin

Chemical name: (1'R,6R,6aR,7R,13S,14S,16R)-8,14-dihydroxy-6',9-dimethoxy-4,10,23-trimethyl-19-oxo-2',3',4',6,7,9',12,13,14,16-decahydro-6aH-spiro[7,13-azano-6,16-(epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1'-pyrido[3,4-b]indol]-5-yl acetate

Molecular formula and molecular mass: $C_{41}H_{44}N_4O_{10}S$; 784.87 g/mol

Structural formula:



Physicochemical properties: lurbinectedin is a white to off-white powder

Lurbinectedin does not show a melting point. Lurbinectedin is sensitive to heat and starts decomposing above 150°C without melting. Lurbinectedin is insoluble or practically insoluble in water, but solubility increases at acidic pH: (very slightly soluble at pH 4, sparingly soluble at pH 2)

NOC/c

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Small Cell Lung Cancer

Table 8. Baseline Characteristics in Study B-005

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study B-005	phase 2 open-label, multi-centre, multi-cohort, single-arm study	3.2 mg/m^2 ZEPZELCA, administered as a 60-minute intravenous infusion repeated every 21 days	105	60 years (40-83 years)	Male: 60% Female: 40%

In a phase 2 open-label, multi-centre, multi-cohort, single-arm study (Study B-005), 105 SCLC patients were treated with 3.2 mg/m^2 ZEPZELCA, administered as a 60-minute intravenous infusion repeated every 21 days (one cycle). Patients received a median of 4 cycles of ZEPZELCA (range 1 to 24 cycles).

A total of 105 treated patients with SCLC who progressed on or after platinum-based chemotherapy were enrolled. The trial excluded patients with central nervous system (CNS) metastases, grade ≥3 dyspnea, daily intermittent oxygen requirement, hepatitis or cirrhosis, and immunocompromised patient. The median age was 60 years (range: 40 to 83 years; 35% were ≥65 years old), 60% were male, 75% were white, 1% were Asian, 1% were Black and 23% were not reported. At baseline, 92% had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 and 92% were former/current smokers. All patients had received prior platinum-based chemotherapy, 71% had received prior radiotherapy and 8% had received immunotherapy in addition to platinum-based chemotherapy. A total of 57% of patients had platinum-sensitive SCLC, defined as chemotherapy free interval (CTFI) ≥90 days and 43% of patients had platinum-resistant SCLC, defined as CTFI <90 days. Out of the 105 patients enrolled in the study, 103 had either loco-regional metastases (n=30 patients) or distant metastases (n=73 patients).

The primary efficacy endpoint was overall response rate (ORR), as assessed by the investigator. Other key efficacy endpoints included duration of response (DOR) as assessed by the investigator and Independent Review Committee (IRC) assessed ORR and DOR.

Table 9 summarizes investigator-assessed and IRC-assessed key efficacy measures in all patients and in platinum-resistant and platinum-sensitive subgroups.

Table 9. Results of Study B-005 in SCLC Cohort

Investigator Assessed Response	All Patients (n=105)	Resistant Disease CTFI <90 days (n=45)	Sensitive Disease CTFI ≥90 days (n=60)
Overall Response Rate (95% CI)	36% (27%, 46%)	22% (11%, 37%)	47% (34%, 60%)
Complete response	0%	0%	0%
Partial response	35%	22%	45%
Duration of Response			
Median in months (95% CI)	5.3 (4.1, 6.2)	4.9 (2.6, 5.6)	5.8 (3.5, 6.4)

Independent Review Committee Assessed Response	All Patients (n=105)	CTFI <90 days (n=45)	CTFI ≥90 days (n=60)
Overall Response Rate (95% CI)	30% (21%, 39%)	13% (5%, 27%)	42% (29%, 55%)
Complete response	0%	0%	0%
Partial response	30%	13%	43%
Duration of Response			
Median in months (95% CI)	5.3 (4.9, 5.9)	5.0 (2.4, NE)	5.5 (4.9, 6.9)

CI, confidence interval; CR, complete response; PR, partial response; IRC, Independent Review Committee; CTFI, chemotherapy free interval; NE, not estimable

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Lurbinectedin was tested in rats, dogs, and non-human primates (NHP) via the intravenous route either as single- or multi-cycle administrations. The maximum tolerated doses (MTDs) in nonclinical species are summarized below:

Table 10. Maximum tolerated dose in Nonclinical Species

Species (Strain)	Sex	MTD mg/kg (mg/m^2)	
		Single-dose	Multi-dose
Rat (Sprague-Dawley)	M	0.2 (1.2)	0.06 (0.36)
	F	0.1 (0.6)	0.03 (0.18)
Dog (Beagle)	M/F	0.03 (0.6)	0.03 (0.6)
Cynomolgus monkey	M/F	0.125-0.167 (1.5-2.0)	0.104-0.125 (1.25-1.5)

F, female; M, male

The primary toxicity of lurbinectedin observed in nonclinical species (rat, dog and NHP) includes severe, reversible and non-cumulative atrophy of the bone marrow, with dose-related leukopenia, as well as thrombocytopenia and anemia. Liver abnormalities (multiple dark areas or swollen liver, increased liver function markers, bile duct damage with necrosis and/or edema, and hepatocellular degeneration/apoptosis and periportal hepatocytic hypertrophy) were also reported. Additional findings were observed in the gastrointestinal tract (mucosal atrophy), kidneys (cortical tubular degeneration and vacuolation), heart (focal, slight to moderate myocardial degeneration and/or necrosis) and at injection sites (perivascular/vascular inflammatory reactions). Full recovery was noted after cessation of dosing for most findings.

Carcinogenicity: Carcinogenicity testing of lurbinectedin has not been performed.

Genotoxicity: Positive genotoxicity results with lurbinectedin were obtained *in vitro* mammalian cell lines. Bacterial reverse mutation assays (Ames) were negative, likely due to lurbinectedin's inability to cross the bacterial wall.

Reproductive and Developmental Toxicology: Studies in pregnant rats administered a single dose of 0.6 mg/m^2 lurbinectedin (approximately equivalent to 20% of the estimated human dose of 3.2 mg/m^2) during the period of organogenesis produced embryo-fetal lethality, and maternal toxicity evidenced by clinical signs, decreases in body weight/body weight gain, and decreased food consumption.

Special Toxicology: *In vitro* evaluation demonstrated no potential phototoxicity of lurbinectedin. In a local tolerance test in rabbits, both intravenous and paravenous administration of lurbinectedin caused slight perivascular and/or vascular chronic inflammatory reactions. The potential for lurbinectedin to induce off-target pharmacological effects is considered unlikely.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr ZEPZELCA®

Lurbinectedin for injection

Read this carefully before you start taking **ZEPZELCA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ZEPZELCA.**

Serious Warnings and Precautions

- ZEPZELCA will be prescribed to you by doctors who are experienced in the use of drugs to treat cancer.
- ZEPZELCA can cause serious side effects including Myelosuppression (a large decrease in the production of blood cells and platelets by the bone marrow). Symptoms include: bleeding, bruising, chills, fatigue, fever, infections, weakness, shortness of breath, or other signs of infection. Tell your healthcare professional right away if you develop new or worsening symptoms.
- ZEPZELCA may harm your unborn baby if you take it while you are pregnant.
- ZEPZELCA can leak out of your vein into the surrounding tissue (extravasation). This may lead to tissue damage after ZEPZELCA is given through a vein in your arm (intravenous administration).
- Your healthcare professional may administer ZEPZELCA through a central venous catheter (tube that is placed into the vein above the heart) to reduce the risk of developing extravasation.

What is ZEPZELCA used for?

For the following indication(s) ZEPZELCA has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- ZEPZELCA is used to treat a type of cancer called Stage III or metastatic small cell lung cancer (SCLC). It is used in adults who have received treatment with chemotherapy that contains platinum and it did not work or is no longer working.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does ZEPZELCA work?

ZEPZELCA works by preventing the cancer cells from growing and spreading to other parts in the body. ZEPZELCA also reduces the ability of other cells to support the growth of the cancer cells. This helps stop the growth of the cancer cells.

What are the ingredients in ZEPZELCA?

Medicinal ingredient: lurbinectedin

Non-medicinal ingredients: lactic acid, sodium hydroxide, sucrose

ZEPZELCA comes in the following dosage forms:

Lyophilized powder, 4 mg / vial for intravenous infusion

Do not use ZEPZELCA if:

- You are allergic to lurbinectedin or any of the other ingredients of ZEPZELCA or the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZEPZELCA. Talk about any health conditions or problems you may have, including if you:

- Have liver problems
- Have kidney problems
- Have any neurological (nervous system) conditions

Other warnings you should know about:

Pregnancy:

- Tell your healthcare professional if you are pregnant or plan to become pregnant.
- ZEPZELCA can harm your unborn baby.
- If you are a woman who could become pregnant:
  - Your healthcare professional should do a pregnancy test before you start treatment with ZEPZELCA.
  - You should use effective birth control (contraception) during treatment with and for 6 months after your final dose of ZEPZELCA.
  - Tell your healthcare professional right away if you become pregnant or think that you are pregnant during treatment with ZEPZELCA.

Males with female partners who are able to become pregnant:

- Use effective birth control during treatment with and for 4 months after your final dose of ZEPZELCA.
- If your partner becomes pregnant while you are taking ZEPZELCA, tell your healthcare professional right away.

Breastfeeding:

- Tell your healthcare professional if you are breastfeeding or plan to breastfeed.
- It is not known if ZEPZELCA passes into your breastmilk. Do not breastfeed during treatment with ZEPZELCA and for 2 weeks after your final dose of ZEPZELCA. Talk to your healthcare provider about

the best way to feed your baby during treatment with ZEPZELCA.

Children:

- ZEPZELCA should not be used in children below 18 years of age.

Rhabdomyolysis (breakdown of damaged muscle):

- ZEPZELCA may cause rhabdomyolysis which is the breakdown of damaged muscle.
- Your healthcare professional will do tests before and during treatment to check for rhabdomyolysis.
- If you get rhabdomyolysis, your healthcare professional will decide which treatments are best for you.

Driving and using machines:

- ZEPZELCA can cause fatigue, weakness, and make you feel unwell. Give yourself time after receiving treatment with ZEPZELCA to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ZEPZELCA:

- Do not eat or drink products or juices containing grapefruit or Seville oranges.
- Do not take St. John's Wort during treatment with ZEPZELCA.
- Statins, a class of medicines used to lower cholesterol.

How to take ZEPZELCA:

- ZEPZELCA will be prepared in an infusion container by a pharmacist and then delivered to the healthcare professional who will administer the medication to you at the hospital.
- ZEPZELCA is given by an intravenous (IV) infusion into a vein over 60 minutes.
- ZEPZELCA is usually given every 21 days.
- Before each treatment with ZEPZELCA, you may receive medicines to help prevent nausea and vomiting or make it less severe.
- Your healthcare professional will decide how long you will continue treatment with ZEPZELCA.
- Your healthcare professional may do certain tests during your treatment with ZEPZELCA to check you for side effects, and to see how well you respond to the treatment.

Usual dose:

The recommended dose of ZEPZELCA is 3.2 mg/m^2 every 21 days. Your doctor will decide how much ZEPZELCA you will receive, and how many treatments you will need.

Overdose:

If you think you, or a person you are caring for, have taken too much ZEPZELCA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss any appointments, call your healthcare professional as soon as possible to reschedule your appointment. It is very important that you do not miss a dose of this medicine.

What are possible side effects from using ZEPZELCA?

These are not all the possible side effects you may have when taking ZEPZELCA. If you experience any side effects not listed here, tell your healthcare professional.

- decreased appetite
- nausea
- vomiting
- diarrhea
- tiredness
- fever
- cough
- dry mouth, altered or impaired sense of taste
- constipation
- weight loss or weight gain
- pain in the abdomen
- pain in chest
- pain in the muscles or bones
- painful swelling or sores inside the mouth
- indigestion
- darkening of the skin
- joint pain
- involuntary contractions of a muscle
- general weakness, fatigue
- dehydration
- headache
- dizziness
- shortness of breath
- skin reaction such as rash, itchiness and dry skin
- skin ulcers
- swelling in the hands or feet
- generally feeling unwell
- sensitivity to light
- difficulty swallowing
- difficulty speaking
- hiccups

ZEPZELCA can cause abnormal blood test results. Your healthcare professional will perform blood tests before and during your treatment. Your doctor will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Low blood counts including neutropenia (low neutrophils), leukopenia (decrease white blood cells), and thrombocytopenia (low platelet counts): fever or any other signs of infection, shortness of breath, tiredness, weakness, unusual bruising or bleeding, pale colored skin		√	
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		√	
Gastrointestinal problems: loss of appetite, nausea or vomiting, pain on the right side of your stomach-area (abdomen)		√	
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, loss of appetite, abnormal blood test results		√	
Liver problems: dark urine, fatigue, loss of appetite, nausea or vomiting, sleepiness, bleeding or bruising, yellowing of the skin or eyes, pain on the upper right side of the stomach area		√	
Pneumonia (infection in the lungs): chest pain when you breathe or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking, chills, nausea, vomiting or diarrhea, shortness of breath		√	
Neuropathy peripheral: weakness, numbness, and pain caused by nerve damage in the arms and legs		√	
COMMON			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
Thrombophlebitis: swelling and redness along a vein which is extremely tender or painful when touched	√		
RARE			
Extravasation (leakage of ZEPZELCA from your vein to the tissue around it): blisters or sores, pain, tenderness, itchiness or burning at the site			√
UNKNOWN			
Rhabdomyolysis (breakdown of damaged muscle): muscle pain, weakness or spasms, red-brown urine			√
Tumour lysis syndrome (the sudden, rapid death of cancer cells due to the treatment): nausea, shortness of breath, irregular heartbeat, heart rhythm disturbances, lack of urination, clouding of urine, muscle spasms or twitching, tiredness and/or joint pain, severe muscle weakness, and seizures. Metabolic disorders (kidney failure, abnormal heartbeat) and abnormal blood tests due to rapid breakdown of cancer cells.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Your healthcare professional will store, prepare, and dispose ZEPZELCA for you.

Store unopened vial in refrigerator at 2°C to 8°C.

If not used immediately after reconstitution or dilution, the diluted solution can be stored prior to administration for up to 24 hours following reconstitution, including infusion time, at either room temperature/ambient light or under refrigerated (2°C to 8°C) conditions.

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

Keep out of reach and sight of children.

If you want more information about ZEPZELCA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.jazzpharma.com, or by calling 1-800-520-5568.

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