PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# Pr**ZYNLONTA®**

Loncastuximab tesirine for injection

Powder for concentrate for solution for infusion, 10 mg, intravenous infusion

Professed Standard

Antineoplastic Agent

ATC Code: L01FX22

ZYNLONTA, indicated for:

- the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, or high-grade B-cell lymphoma, who have received two or more lines of systemic therapy and have previously received or are unable to receive CAR-T cell 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 ZYNLONTA 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**

None at the time of the most recent authorization.

**TABLE OF CONTENTS**

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

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

ZYNLONTA® (loncastuximab tesirine) as monotherapy is indicated for:

- the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, or high-grade B-cell lymphoma, who have received two or more lines of systemic therapy and have previously received or are unable to receive CAR-T cell therapy.

### 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 clinically meaningful differences in safety or efficacy were observed between geriatric patients and younger patients (see 4.2 Recommended Dosage and Dosage Adjustment, 7.1.4 Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions).

## 2 CONTRAINDICATIONS

ZYNLONTA is contraindicated in patients who are hypersensitive to this drug or to any of the ingredients in the formulation, including any non-medicinal ingredient, or component of the container (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

ZYNLONTA should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients.

Reconstitute and further dilute ZYNLONTA prior to intravenous infusion (see 4.3 Reconstitution).

Premedication with Dexamethasone

Unless contraindicated, administer dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before administering ZYNLONTA. If dexamethasone administration does not begin the day before ZYNLONTA, oral or intravenous dexamethasone should begin at least 2 hours prior to administration.

### 4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

ZYNLONTA is an intravenous infusion administered over 30 minutes on Day 1 of each 21-

day cycle (every 3 weeks). The recommended dose of ZYNLONTA is:

- 0.15 mg/kg every 3 weeks for 2 cycles, followed by
- 0.075 mg/kg every 3 weeks for subsequent cycles

For patients with a body mass index (BMI) ≥35 kg/$m^2$, calculate the dose based on adjusted body weight (ABW) as follows: ABW in kg = 35 kg/$m^2$ x (height in meters)$^2$.

Dose Adjustment

Table 1 outlines the recommended dose modification for adverse reactions.

**Table 1: ZYNLONTA Dose Modification for Hematologic and Non-hematologic Adverse Reactions**

| Adverse Reactions | Severity[a] | Dose Modification |
|---|---|---|
| **Hematologic Adverse Reactions** | | |
| Neutropenia | Absolute neutrophil count less than 1 x $10^9$/L | Withhold ZYNLONTA until neutrophil count returns to 1 x $10^9$/L or higher |
| Thrombocytopenia | Platelet count less than 50,000/µL | Withhold ZYNLONTA until platelet count returns to 50,000/µL or higher |
| **Non-hematologic Adverse Reactions** | | |
| Edema or Effusion | Grade 2[a] or higher | Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less |
| Other Adverse Reactions | Grade 3[a] or higher | Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less |

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

Dose Delays / Reductions

If dosing is delayed by more than 3 weeks due to toxicity related to ZYNLONTA, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation. Note: If toxicity requires dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the planned dose of 0.075 mg/kg for Cycle 3.

Special Populations

Pediatrics (<18 years of age):

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

Geriatrics (≥65 years of age):

No dose adjustment is required in patients ≥65 years of age (see 7.1.4 Geriatrics).

Renal impairment:

No dose adjustment is required for patients with mild (creatinine clearance [CrCl] ≥60 using the Cockcroft-Gault equation) and to moderate (CrCl ≥30 and <60 mL/min) renal impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions). ZYNLONTA has not been

studied in patients with severe renal impairment (CrCl 15 to 29 mL/min) or end-stage renal disease with or without hemodialysis.

Hepatic impairment:

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin >1 to 1.5 × ULN and any AST) (see 10.3 Pharmacokinetics, Special Populations and Conditions).

ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

In patients with hepatic impairment, monitoring for potentially increased incidence of adverse reactions and modifying the ZYNLONTA dosage in the event of adverse reactions are recommended.

### 4.3 Reconstitution

Reconstitute and further dilute ZYNLONTA prior to intravenous infusion. Use appropriate aseptic technique.

ZYNLONTA is a cytotoxic drug. Follow applicable special handling and disposal procedures (see 11 STORAGE, STABILITY AND DISPOSAL and 12 SPECIAL HANDLING INSTRUCTIONS).

Dose calculation

Calculate the total dose (mg) required based on the patient's weight and prescribed dose. See 4.2 Recommended Dose and Dosage Adjustment.

Reconstitution of Lyophilized ZYNLONTA

- Reconstitute each ZYNLONTA vial using 2.2 mL of **Sterile Water for Injection** with the stream directed toward the inside wall of the vial to obtain a final concentration of 5 mg/mL.
- Swirl the vial gently until the powder is completely dissolved. *Do not shake. Do not expose to direct sunlight.*
- Inspect the reconstituted solution for particulate matter and discoloration. The solution should appear clear to slightly opalescent, colourless to slightly yellow. Do not use if the reconstituted solution is discolored, is cloudy, or contains visible particulates.
- Use reconstituted ZYNLONTA immediately. If not used immediately, store the reconstituted solution in the vial for up to 4 hours refrigerated at 2°C to 8°C or room temperature 20°C to 25°C . *Do not freeze.*
- The product does not contain a preservative. Discard unused vial after reconstitution if the recommended storage time is exceeded.

Dilution in Infusion Bag

- Withdraw the required volume of reconstituted solution from the ZYNLONTA vial using a sterile syringe. Discard any unused portion left in the vial.
- Add the calculated dose volume of ZYNLONTA solution into a 50 mL infusion bag of **5% Dextrose Injection**.

- Gently mix the intravenous bag by slowly inverting the bag. *Do not shake. Do not expose to direct sunlight.*
- If not used immediately, store the diluted ZYNLONTA infusion solution refrigerated at 2°C to 8°C for up to 24 hours or at room temperature 20°C to 25°C for up to 8 hours. *Do not freeze*. Discard diluted infusion bag if storage time exceeds these limits.
- No incompatibilities have been observed between ZYNLONTA and intravenous infusion bags with product-contacting materials of polyvinylchloride (PVC), polyolefin (PO), and PAB® (copolymer of ethylene and propylene).

### 4.4 Administration

- Administer by intravenous infusion over 30 minutes using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2- or 0.22-micron pore size) and catheter.
- Extravasation of ZYNLONTA has been associated with irritation, swelling, pain, and/or tissue damage, which may be severe. The infusion site should be monitored for possible subcutaneous infiltration during drug administration.
- Do not mix ZYNLONTA with or administer as an infusion with other drugs.

### 4.5 Missed Dose

Delayed or Missed Doses

If a planned dose of ZYNLONTA is missed, it should be administered as soon as possible, and the schedule of administration should be adjusted to maintain a 3-week interval between doses.

## 5 OVERDOSAGE

There is limited information on overdosage with loncastuximab tesirine. In clinical studies, the highest dose administered was 0.2 mg/kg. The incidence of severe adverse events increased with increasing doses. In the event of overdosage, patients should be closely monitored, and symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied. There is no antidote for loncastuximab tesirine.

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

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

**Table 2: Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Intravenous | Powder for concentrate for solution for infusion/ 10 mg/vial. | histidine monohydrochloride, L-histidine, polysorbate 20, and sucrose |

ZYNLONTA for injection is supplied in single use vials as a sterile, white to off-white, preservative free, lyophilized powder, with a cake-like appearance, for intravenous infusion after reconstitution and dilution.

After reconstitution with 2.2 mL Sterile Water for Injection the final concentration is 5 mg/mL with a pH of approximately 6.0.

## 7 WARNINGS AND PRECAUTIONS

### General

Effusion and Edema

Serious effusion and edema have been reported in patients treated with ZYNLONTA (see 8 ADVERSE REACTIONS).

Patients should be monitored for new or worsening edema or effusion. ZYNLONTA should be withheld for Grade 2 or greater edema or effusion until the toxicity resolves. Diagnostic imaging should be considered in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsening dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Appropriate medical management for edema or effusion should be instituted (see 4.2 Recommended Dosage and Dosage Adjustment).

### Driving and Operating Machinery

Fatigue has been reported in some patients taking ZYNLONTA and this should be taken into account when driving or using machines.

### Hematologic

Myelosuppression

Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia (see 8 ADVERSE REACTIONS).

Complete blood cell counts should be monitored throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA (see 4.2 Recommended Dosage and Dosage Adjustment). Prophylactic granulocyte colony-stimulating factor administration should be considered, as applicable.

**Immune**

Infections

Fatal and serious infections, including opportunistic infections, have been reported in patients treated with ZYNLONTA. In clinical trials, the most frequent Grade ≥3 infections included sepsis and pneumonia (see 8 ADVERSE REACTIONS).

Patients should be monitored for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, ZYNLONTA should be withheld until infection has resolved (see 4.2 Recommended Dose and Dosage Adjustment).

**Reproductive Health: Female and Male Potential**

Females

ZYNLONTA may cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199), which affects actively dividing cells. Pregnant women should be advised of the potential risk to the fetus.

Advise women of reproductive potential to use effective contraception during treatment and for 10 months after the last dose (see 7.1.1 Pregnant Women).

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 7 months after the last dose.

- **Fertility**

In non-clinical studies, ZYNLONTA was associated with irreversible testicular toxicity so may impair male reproductive function and fertility (see 16 NON-CLINICAL TOXICOLOGY).

Therefore, men being treated with this medicine should be advised to consider having sperm samples preserved and stored before initiating treatment.

- **Teratogenic Risk**

The cytotoxic component of ZYNLONTA, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

**Skin**

Photosensitivity and Cutaneous Reactions

Serious cutaneous reactions have been reported in patients treated with ZYNLONTA (see 8 ADVERSE REACTIONS).

Patients should be monitored for new or worsening cutaneous reactions, including photosensitivity reactions. ZYNLONTA should be withheld for severe (Grade 3) cutaneous reactions until resolution (see 4.2 Recommended Dose and Dosage Adjustment). Patients should be advised to minimize or avoid exposure to direct natural or artificial sunlight

including exposure through glass windows. Patients should be instructed to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered (see 16 NON-CLINICAL TOXICOLOGY).

### 7.1 Special Populations

#### 7.1.1 Pregnant Women

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells (see 10.1 Mechanism of Action and 16 NON-CLINICAL TOXICOLOGY). There are no data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. ZYNLONTA is not recommended during pregnancy. ZYNLONTA is not recommended in women of childbearing potential not using contraception.

Advise pregnant women of the potential risk to a fetus.

Pregnancy testing is advised prior to initiating ZYNLONTA.

#### 7.1.2 Breast-feeding

There are no data on the presence of ZYNLONTA in human milk, the effects on the breastfed child, or milk production. A risk for breastfed children cannot be excluded.

Because of the potential for serious adverse reactions in breastfed children, advise women not to breast-feed during treatment with ZYNLONTA and for at least 3 months after the last dose.

#### 7.1.3 Pediatrics

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

#### 7.1.4 Geriatrics

**Geriatrics (≥ 65 years of age):** Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older (see 14 CLINICAL TRIALS). No clinical differences in safety or efficacy were observed between these patients and younger patients.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The safety of ZYNLONTA administered as a single agent at an initial starting dose of 0.15 mg/kg for the first two cycles, followed by 0.075 mg/kg for the subsequent cycles, was investigated in 145 patients with relapsed or refractory DLBCL in Study ADCT-402-201 (LOTIS-2). The median

duration of treatment was 45 days (range: 1 to 569 days). The median number of cycles was 3 (range 1 to 26 cycles) with 34% of patients receiving five or more cycles.

The most frequently (≥ 20%) reported adverse reactions with ZYNLONTA were gamma-glutamyltransferase (GGT) increased (42.1%), neutropenia (40%), thrombocytopenia (33.1%), fatigue (27.6%), anemia (26.2%), nausea (23.4%), cough (22.8%), blood alkaline phosphatase increased (20%) and peripheral edema (20%).

The most frequent (≥ 2%) serious adverse reactions were febrile neutropenia (3.4%), pyrexia (2.8%), abdominal pain (2.1%), and pleural effusion (2.1%). Treatment-emergent events of fatal infections occurred in 2.1% of patients.

Dose interruption due to adverse reactions occurred in 51% of patients. The most frequent (≥ 5%) adverse reactions leading to dose delay were GGT increased (21.4%), neutropenia (12.4%) and thrombocytopenia (9%).

Dose reductions due to adverse reactions occurred in 6.9% of patients. The adverse reaction leading to dose reductions reported in two or more patients was GGT increased (3.4%).

Permanent treatment discontinuation due to adverse reactions occurred in 24.8% of patients. The most frequent (≥ 2%) adverse reactions leading to treatment withdrawal were GGT increased (12.4%), peripheral edema (2.8%), localized edema (2.1%), and pleural effusion (2.1%).

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect the frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Table 3 summarizes the adverse reactions that occurred in at least 5% of patients treated with ZYNLONTA in Study ADCT-402-201 (LOTIS-2).

**Table 3: Adverse Reactions Reported in at Least 5% of Patients with Relapsed/Refractory DLBCL Treated with ZYNLONTA in LOTIS-2.**

| System Organ Class<br>Preferred Term[a] | ZYNLONTA (N=145) | | |
|---|---|---|---|
| | All Grades N (%) | Grade 3 N (%) | Grade 4 N (%) |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia | 58 (40.0) | 14 (9.7) | 24 (16.6) |
| Thrombocytopenia | 48 (33.1) | 18 (12.4) | 8 (5.5) |
| Anemia | 38 (26.2) | 15 (10.3) | 0 |
| **Gastrointestinal disorders** | | | |
| Nausea | 34 (23.4) | 0 | 0 |
| Diarrhea | 25 (17.2) | 3(2.1) | 0 |
| Abdominal pain[b] | 21 (14.5) | 3 (2.1) | 1 (0.7) |
| Vomiting | 19 (13.1) | 0 | 0 |
| Constipation | 17 (11.7) | 0 | 0 |
| **General disorders and administration site reactions** | | | |
| Fatigue | 40 (27.6) | 2 (1.4) | 0 |
| Edema peripheral | 29 (20.0) | 2 (1.4) | 0 |
| Pyrexia | 28 (19.3) | 2 (1.4) | 0 |
| Asthenia | 14 (9.7) | 0 | 0 |
| **Investigations** | | | |
| Gamma-glutamyltransferase increased | 61 (42.1) | 33 (15.3) | 4 (1.9) |
| Blood alkaline phosphatase increased | 29 (20.0) | 1 (0.7) | 0 |
| Aspartate aminotransferase increased | 23 (15.9) | 1 (0.7) | 0 |
| Alanine aminotransferase increased | 22 (15.2) | 4 (2.8) | 0 |
| **Metabolism and nutrition disorders** | | | |
| Decreased appetite | 22 (15.2) | 0 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Pain in extremity | 9 (6.2) | 0 | 0 |
| Back pain | 9 (6.2) | 0 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Cough | 33 (22.8) | 1 (0.7) | 0 |
| Dyspnea[c] | 19 (13.1) | 2 (1.4) | 0 |
| Pleural effusion | 16 (11.0) | 3 (2.1) | 0 |
| **Skin and subcutaneous tissue disorders** | | | |
| Rash | 19 (13.1) | 1 (0.7) | 0 |
| Pruritus | 19 (13.1) | 0 | 0 |
| Erythema | 15 (10.3) | 1 (0.7) | 0 |
| Photosensitivity reaction | 15 (10.3) | 3 (2.1) | 0 |
| Maculopapular rash | 8 (5.5) | 1 (0.7) | 0 |

[a]MedDRA Version 22.0, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

[b] Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort.
[c] Includes dyspnea, dyspnea exertional.

Description of Selected Adverse Reactions (LOTIS-2)

*Effusion or Edema*
Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade ≥3 edema or effusion occurred in 4.8% of patients. Grade 3 or 4 pericardial effusion occurred in 2.1% of patients. Grade 3 pleural effusion, ascites, and peripheral edema occurred in 2.1%, 2.1%, and 1.4% of patients, respectively (see 7 WARNINGS AND PRECAUTIONS, Effusion and Edema).

*Myelosuppression*
Treatment with ZYNLONTA can cause severe myelosuppression. Grade 3 or 4 neutropenia occurred in 26.2%, Grade 3 or 4 thrombocytopenia in 17.9%, and Grade 3 or 4 anemia in 10.3% of patients. Febrile neutropenia occurred in 3.4% of patients (see7 WARNINGS AND PRECAUTIONS, Myelosuppression). Thrombocytopenia and neutropenia led to discontinuation of treatment in 0.7% of patients, respectively.

*Infections*
Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 9.0% of patients, with fatal infections occurring in 2.1%. The most frequent Grade ≥3 infections included sepsis and pneumonia (see 7 WARNINGS AND PRECAUTIONS, Infections).

*Cutaneous Reactions*
Severe cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4.1% and included photosensitivity reaction (2.1%), rash (0.7%), rash pustular (0.7%), rash maculo-papular (0.7%), and erythema (0.7%) (see 7 WARNINGS AND PRECAUTIONS, Photosensitivity and Cutaneous Reactions). Two (2) patients (1.4%) discontinued ZYNLONTA due to Grade 1-2 cutaneous reactions.

### 8.3 Less Common Clinical Trial Adverse Reactions

Less common adverse reactions reported in <5% of patients with relapsed/refractory DLBCL treated with ZYNLONTA are shown below.

*Blood and lymphatic system disorders:* febrile neutropenia

*Cardiac disorders:* pericardial effusion; pericarditis

*Gastrointestinal disorders:* ascites

*General disorders and administration site reactions:* face edema; non-cardiac chest pain; peripheral swelling; swelling; generalized edema; edema

*Infections and infestations:* upper respiratory tract infection; lower respiratory tract infection; pneumonia[a]; pustular rash; sepsis

*Injury, poisoning and procedural complications:* infusion-related reactions[b]

*Metabolism and nutrition disorders:* fluid retention; fluid overload

*Musculoskeletal and connective tissue disorders:* neck pain; musculoskeletal pain; myalgia; musculoskeletal chest pain; musculoskeletal discomfort; limb discomfort

*Nervous system disorders:* lethargy

*Respiratory, thoracic and mediastinal disorders:* pneumonitis; pleuritis

*Skin and subcutaneous tissue disorders:* skin hyperpigmentation; pruritic rash; swelling face; bullous dermatitis

[a] Includes pneumonia and lung infection.
[b] Symptoms of infusion-related reactions include nausea, drug hypersensitivity, swelling of face, pruritus and flushing.

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

### Clinical Trial Findings

The following table summarizes treatment-emergent shifts from baseline in laboratory abnormalities in LOTIS-2.

**Table 4: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in LOTIS-2.**

| Laboratory Abnormality | ZYNLONTA | |
|---|---|---|
| | All Grades[a] N (%)[c] | Grade 3 or Grade 4[b] N (%)[c] |
| **Hematologic** | | |
| Platelets decreased | 84 (58.3) | 25 (17.4) |
| Neutrophils decreased | 75 (52.1) | 43 (29.9) |
| Hemoglobin decreased | 75 (51.7) | 16 (11.0) |
| **Chemistry** | | |
| Gamma-glutamyltransferase increased | 82 (57.3) | 31 (21.7) |
| Glucose increased | 69 (48.3) | 11 (7.7) |
| Aspartate aminotransferase increased | 60 (41.7) | 1 (0.7) |
| Albumin decreased | 53 (36.8) | 1 (0.7) |
| Alanine aminotransferase increased | 49 (33.8) | 5 (3.4) |

[a] Includes all patients where the maximum post-baseline Grade > baseline Grade.
[b] Includes all patients who had a baseline value ≤ Grade 2 and who worsened to ≥ Grade 3 post-baseline.
[c] Numerator varies between 143 and 145 patients, reflecting available baseline and post-baseline data. Percentages are based on the number of patients who have both a baseline and a post-baseline value.

### 8.5 Post-Market Adverse Reactions

**Skin and Subcutaneous Tissue Disorders**: telangiectasia; blister; rash vesicular.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

No drug interaction studies have been performed in humans for loncastuximab tesirine, free tesirine, SG3199 and related metabolites. No clinically important PK interactions are expected.

*In Vitro* Studies

*Cytochrome P450 (CYP) Enzymes*: SG3199 does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 at clinically relevant unconjugated SG3199 concentrations.

*Transporter Systems*: SG3199 is a substrate of P-glycoprotein (P-gp), but not a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP)1B1, or organic cation transporter (OCT)1.

At clinically relevant concentrations, unconjugated SG3199 does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, OCT2, OCT1, multi-antimicrobial extrusion protein (MATE)1, MATE2-K, or bile salt export pump (BSEP).

### 9.3 Drug-Behavioural Interactions

Not applicable.

### 9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Loncastuximab tesirine is an antibody-drug conjugate (ADC) targeting CD19 (see 13 PHARMACEUTICAL INFORMATION). The monoclonal IgG1 kappa antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. The small molecule component is SG3199, a pyrrolobenzodiazepine (PBD) dimer and alkylating agent.

Upon binding to CD19, loncastuximab tesirine is internalized followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death.

### 10.2 Pharmacodynamics

Higher loncastuximab tesirine exposure in Cycle 1 was associated with higher efficacy over the dose range of 0.015-0.2 mg/kg (0.1 to 1.33 times the maximum recommended dose). Higher loncastuximab tesirine exposure in Cycle 1 was associated with higher incidence of some Grade ≥2 adverse reactions, including skin and nail reactions, and liver function test abnormalities including increased gamma-glutamyltransferase.

*Cardiac electrophysiology*

At the maximum recommended therapeutic dose of 0.15 mg/kg during Cycle 1 and Cycle 2, loncastuximab tesirine does not cause large mean increases (i.e., >20 msec) in the QTc interval.

### 10.3 Pharmacokinetics

**Table 5: Summary of Pharmacokinetic Parameters for Conjugated Antibody during Cycles 1, 2 and 3 for Patients Treated with Loncastuximab Tesirine 0.15 mg/kg Q3Wx 2, Followed by 0.075 mg/kg Q3W in LOTIS-2.**

| Cycle | Cmax# (ng/mL) | AUClast (day*ng/mL) | AUC# (day*ng/mL) | Thalf (day) | CL# (L/day) | Vss (L) |
|---|---|---|---|---|---|---|
| 1 | 2436 (38.7) [143] | 16016 (105) [144] | 19819 (53.7) [32] | 8.85 (53.6) [32] | 0.458 (48.4) [32] | 4.24 (39.9) [32] |
| 2 | 2736 (35.6) [118] | 23113 (81.0) [117] | 26902 (33.4) [99] | 15.3 (31.7) [89] | 0.331 (32.0) [99] | 6.42 (36.7) [89] |
| 3 | 1694 (47.6) [83] | - | - | - | - | - |

Data were presented in geometric mean (CV %) [N].
Estimated with a non-compartmental analysis.
Abbreviation: AUC#= area under the concentration-time curve from time 0 to infinity (AUCinf) for cycle 1 and area under the concentration-time curve from time 0 to end of dosing interval (AUCtau) for cycle 2; AUClast=area under the concentration-time curve from time 0 to last measurable timepoint in respective cycle; Cmax#=maximum observed concentration for cycles 1 and 2 or concentration at end-of-infusion for cycle 3; CL#=apparent clearance for cycle 1 and apparent clearance at steady state for cycle 2; CV%=geometric percent coefficient of variation; N=number of patients; Q3W=every three weeks; Thalf=apparent terminal half-life; Vss =apparent volume of distribution at steady state; -= not available.

**Absorption**

ZYNLONTA is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

**Distribution**

The geometric mean (CV%) loncastuximab tesirine volume of distribution was 7.14 (22.9%) L.

**Metabolism**

The monoclonal antibody portion of loncastuximab tesirine is expected to be metabolized into small peptides by catabolic pathways. The small molecule cytotoxin, SG3199, is metabolized by CYP3A4/5 *in vitro*.

**Elimination**

The estimated clearance parameter of the conjugated antibody decreased from cycle 1 to cycle 2.

The major excretion pathways of the warhead SG3199 have not been studied in humans. Data collected in an animal model (rat) showed predominantly fecal elimination with only minimal renal excretion in the low % range.

**Dose-proportionality**

The AUCinf parameter of the conjugated antibody is dose-proportional from 0.015 to 0.200 mg/mL.

**Special Populations and Conditions**

A population PK covariate analysis could not detect any clinically significant differences in the pharmacokinetic parameters of loncastuximab tesirine based on the covariates of age (20-94 years), sex, race (White vs. Black), body weight (42.1 to 160.5 kg), ECOG status (0 to 2) or mild to moderate renal impairment (CLcr 30 to <90 mL/min using the Cockcroft-Gault equation).

- **Hepatic Impairment:** In the final population PK model, estimates in the category of mild hepatic impairment, defined as total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 × ULN and any AST suggested an increase in the exposure PK parameters of unconjugated SG3199, however there was no clinically significant effect on loncastuximab tesirine pharmacokinetic parameters.

  ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin>1.5 × ULN and any AST).

- **Renal Insufficiency**: In the final population PK model, the estimates of the clearance parameter of loncastuximab tesirine in patients with mild to moderate renal impairment (CLcr 30 to <90 mL/min using the Cockcroft-Gault equation) was not significantly different from patients with normal renal function.

  For SG3199, data collected in an animal model (rat) show minimal renal excretion. No clinical data are available.

## 11 STORAGE, STABILITY AND DISPOSAL

### Storage and Stability

Store refrigerated at 2°C to 8°C in original carton to protect from light. *Do not freeze. Do not shake.*

Reconstituted solution

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 4 hours refrigerated (2°C - 8°C) or 4 hours at room temperature (20°C - 25°C). Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 4 hours refrigerated (2°C - 8°C) or 4 hours at room temperature (20°C - 25°C).

Diluted solution

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours refrigerated (2°C - 8°C) or 8 hours at room temperature (20°C - 25°C). Chemical and physical in-use stability of the prepared solution for infusion has been demonstrated for up to 24 hours at room temperature (20°C - 25°C).

Do not use the medicinal product if the storage conditions exceed the limits.

### Disposal

See 12 SPECIAL HANDLING AND INSTRUCTIONS.

## 12 SPECIAL HANDLING INSTRUCTIONS

ZYNLONTA is a cytotoxic drug. Procedures for proper handling and disposal of antineoplastic and cytotoxic medicinal products should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

### Drug Substance

Proper name: loncastuximab tesirine

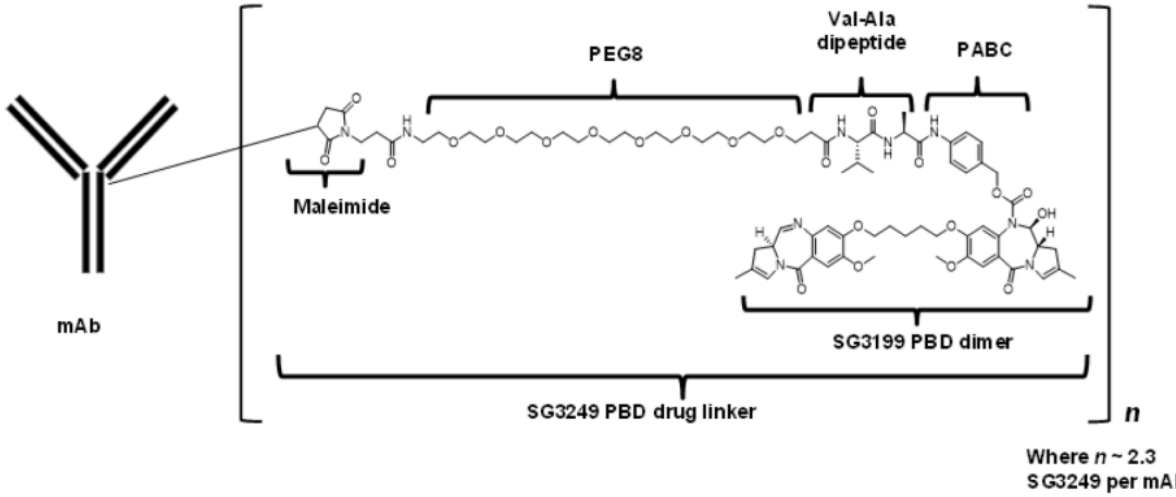
Chemical name: Immunoglobulin IG, (anti-[human CD19 antigen]) (humanized clone RB4v1.2 γl-chain), disulfide with humanized clone RB4v1.2 κ-chain, dimer, bis (thioether) with N-(31-[2, 5-dihydro-2, 5-dioxo-1H-pyrrol-1-yl]-1, 29-dioxo-4, 7, 10, 13, 16, 19, 22, 25-octaoxa-28 azahentriacont-1- yl)-L-valyl-N-[4-[[[[(11S, 11aS)-8-[[5-[[(l1aS)- 5,11a-dihydro-7-methoxy-2-

methyl-5-oxo-1Hpyrrolo[2,1-c][1,4] benzodiazepin-8-yl]oxy]pentyl]oxy]-11, 11a-dihydro-11-hydroxy-7-methoxy-2-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10 (5H)-yl]carbonyl]oxy]methyl]phenyl]-L-alaninamide

Molecular formula and molecular mass: $C_{6544}H_{10048}N_{1718}O_{2064}S_{52}$

150 kiloDalton (kDa)

Structural formula:




Note: The representation shows one molecule of SG3249 covalently bound to the antibody. SG3249 comprises the PBD dimer SG3199 and all linker components, including maleimide, polyethylene glycol PEG8, a cathepsin-cleavable Valine-Alanine linker and a para-aminobenzyl carbamate self-immolating group. In the drug product, the average number of SG3249 molecules covalently bound to the antibody is approximately two.
Ala = alanine; CD19 = cluster of differentiation 19; mAb = monoclonal antibody; PABC = para-aminobenzyl carbamate; PBD = pyrrolobenzodiazepine; PEG = polyethylene glycol; Val = valine.

Physicochemical properties: Loncastuximab tesirine is a CD19-directed antibody and alkylating agent conjugate, consisting of a humanized IgG1 kappa monoclonal antibody conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent, through a protease-cleavable valine-alanine linker. SG3199 attached to the linker is designated as SG3249, also known as tesirine. Loncastuximab tesirine has an approximate molecular weight of 151 kDa. An average of 2.3 molecules of SG3249 are attached to each antibody molecule. Loncastuximab tesirine is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

**Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) after Two or More Lines of Systemic Therapy**

Trial Design and Study Demographics

**Table 6: Summary of Study Design and Patient Demographics in Clinical Trial of Relapsed or Refractory Large B-cell Lymphoma**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex n (%) |
|---|---|---|---|---|---|
| ADCT-402-201 | Phase 2, multi-centre, open-label, single-arm study | 0.15 mg/kg administered every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles<br>Intravenous administration<br>30-minute infusion | n = 145 | 62.7 years<br>(23 – 94) | Female: 60 (41%)<br>Male: 85 (59%) |

The efficacy of ZYNLONTA was evaluated in ADCT-402-201 (LOTIS-2), an open-label, single-arm study in 145 adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior lines of systemic therapy. Eligible patients had measurable disease as defined by the 2014 Lugano classification, adequate organ functions and ECOG performance status 0-2. The study excluded patients with bulky disease (defined as any tumour ≥10 cm in the longest dimension), active central nervous system lymphoma, Burkitt's lymphoma, or clinically significant third space fluid accumulation. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles. Patients received treatment for up to 1 year, or beyond if they were clinically benefitting, or until progressive disease or unacceptable toxicity.

Of the 145 patients enrolled, the median age was 66 years (range 23 to 94), with 14% of patients 75 years of age and older. Ninety-four percent (94%) of patients had an ECOG performance status of 0 to 1. The diagnosis was DLBCL NOS in 88% of patients (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma (with MYC and BCL2 and/or BCL6 rearrangements) in 7%. The median number of prior lines of systemic therapies was 3 (range 2 to 7); 43% of patients received 2 prior lines, 23% received 3 prior lines, and 33% received more than 3 prior lines. Twenty percent (20%) of patients had primary refractory disease, 17% received prior stem cell transplant, and 10% received prior chimeric antigen receptor (CAR) T-cell therapy.

Study Results

The efficacy of ZYNLONTA was evaluated on the basis of overall response rate (ORR) defined as the proportion of patients who achieved either complete response (CR) or partial response (PR) as best overall response (BOR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria. The median follow-up time was 7.8 months (range 0.3 to 42.6).

**Table 77: Efficacy Results in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma in LOTIS-2**

| **Efficacy parameter** | **ZYNLONTA N = 145** |
|---|---|
| **Primary Endpoint** | |
| Overall response rate[a], n (%) [95% CI] | 70 (48.3%) [39.9, 56.7] |
| Complete response rate[a], n (%) [95% CI] | 36 (24.8%) [18.0, 32.7] |
| **Secondary Endpoints** | |
| Median time to first response[a], days (range) | 41.0 (35, 247) |
| Median duration of response[b], months [95% CI] | N=70 13.4 [6.9, NE] |
| Median duration of complete response[a], months [95% CI] | N=36 NE, (NE, NE) |

CI = confidence interval, NE = not estimable

[a] Assessed by independent review committee using Lugano 2014 criteria.

[b] DOR was defined for patients with CR or PR as the interval between the date of initial documentation of a response and the date of the first documented evidence of progressive disease (PD) based on independent radiographic assessment or death, whichever occurred first. If PD or death was not observed, the DOR was censored at the last valid disease assessment on or before the start of subsequent anticancer therapy.

Among patients achieving a complete response, the probability of continued response was 64.4% at 9 months.

Post CAR-T Subgroup

Among patients who had previously received CAR-T cell therapy, the ORR was 42.9% and the CRR was 21.4%.

### 14.4 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies to ZYNLONTA in other studies or to other products may be misleading.

In LOTIS-2, 1 of 145 patients tested positive for antibodies against ZYNLONTA after treatment. The potential effect of anti-drug antibodies to ZYNLONTA on pharmacokinetics, efficacy, or safety is unknown.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**General Toxicology:**

Inflammatory-mediated toxicities associated with PBDs have been observed at low incidence in animals. In repeat-dose toxicity studies in cynomolgus monkeys, intravenous administration of loncastuximab tesirine was associated with potential inflammatory mediated-toxicities, including in the lungs and kidneys. Renal toxicity included increasing kidney weights and nephropathy with variable reversible inflammation and fibrosis.

Black skin spots potentially related to phototoxicity were observed in cynomolgus monkeys and were still present after a 12-week treatment-free period.

**Carcinogenicity:**

Carcinogenicity studies have not been conducted with loncastuximab tesirine or SG3199.

**Genotoxicity:**

SG3199 was genotoxic in an *in vitro* micronucleus test and a chromosome aberration assay using human lymphocytes through a clastogenic mechanism. These results are consistent with the pharmacological effect of SG3199 as a covalent DNA crosslinking agent. Results of a bacterial reverse mutation assay (Ames test) were inconclusive due to cytotoxicity.

**Reproductive and Developmental Toxicology:**

Fertility studies have not been conducted with loncastuximab tesirine. Results from repeat-dose toxicity studies with intravenous administration of loncastuximab tesirine in cynomolgus monkeys indicate the potential for impaired male reproductive function and fertility. Administration of loncastuximab tesirine to cynomolgus monkeys every 3 weeks at 0.6 mg/kg for a total of 2 doses, or every 3 weeks at 0.3 mg/kg for 13 weeks for a total of 5 doses resulted in adverse findings that included decreased weight and/or size of the testes and epididymis, atrophy of the seminiferous tubules, germ cell degeneration, and/or reduced epididymal sperm content. The dose of 0.3 mg/kg in animals results in an exposure (AUC) that is approximately 3 times the exposure at the maximum recommended human dose [MRHD] of 0.15 mg/kg. Findings were not reversible at the end of the 12-week recovery period following 4 or 13 weeks of dosing.

No dedicated reproductive toxicity studies in animals have been conducted with loncastuximab tesirine. However, the cytotoxic component of loncastuximab tesirine, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryo-fetal toxicity and teratogenicity.

**PATIENT MEDICATION INFORMATION**

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrZYNLONTA®**
**Loncastuximab tesirine for injection**
**Powder for concentrate for solution for infusion**

Read this carefully before you start taking **ZYNLONTA** 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 **ZYNLONTA**.

**What is ZYNLONTA used for?**

For the following indication ZYNLONTA 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.

ZYNLONTA is used to treat adults with a certain type of cancer called diffuse large B-cell lymphoma who have already received CAR-T cell treatment or who are unable to receive CAR-T cell treatment. It is used when:

- the cancer has come back (relapsed), or
- the cancer did not respond to previous treatment (refractory).

Large B-cell lymphoma is a cancer that develops from a type of white blood cell called B-lymphocytes (also called B-cells). In large B-cell lymphoma, B-cells multiply in an uncontrolled manner and build up in your body.

**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, or 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 ZYNLONTA work?**

ZYNLONTA consist of 2 parts; an antibody (a type of protein designed to recognize and attach

to a specific target) and a cytotoxic agent (a medicine able to kill cells, including cancer cells). The antibody in this medicine is designed to attach to a protein, called CD19, that is found on the surface of B cells. When the antibody binds to these cells, including the cancer cells, the medicine enters the cells and kills them.

**What are the ingredients in ZYNLONTA?**

Medicinal ingredients: loncastuximab tesirine

Non-medicinal ingredients: histidine monohydrochloride, L-histidine, polysorbate 20, sucrose

**ZYNLONTA comes in the following dosage forms:**

ZYNLONTA is available as powder for concentrate for solution for infusion in a single-use vial containing 10 mg.

**Do not use ZYNLONTA if:**

- if you are allergic to loncastuximab tesirine or any of the other ingredients of this medicine (listed in "What are the ingredients in ZYNLONTA?"). Talk to your healthcare professional if you are not sure.

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

- have an active infection or have had one recently
- have liver problems; symptoms may include skin and eyes appearing yellowish (jaundice). Your doctor will monitor you for side effects during treatment.
- are pregnant or plan to become pregnant. ZYNLONTA can harm your unborn baby. You should avoid getting pregnant if you are taking this medicine. **Tell your doctor immediately** if you become pregnant or think that you are pregnant during treatment with ZYNLONTA.

**Other warnings you should know about:**

Tell your doctor or nurse straight away if you have any of the following serious side effects.

*Infections*
Serious infections, including infections that can cause death, have occurred in people treated with ZYNLONTA. **Tell you healthcare professional immediately** if you have new or worsening signs or symptoms of infection, such as:

- fever
- chills or shivering
- flu-like symptoms (cough, tiredness or feeling weak, and body aches)
- severe headache
- cuts or scrapes that are red, warm, swollen, or painful

*Fluid retention*
Your body may hold too much fluid during treatment with ZYNLONTA. This can be serious. You can get swelling in various parts of your body including your hands, feet and abdomen, or around internal organs such as your heart and lungs. **Tell your healthcare professional immediately** if you notice any of the following signs and symptoms:

- chest pain
- difficulty breathing
- swelling and pain in the abdomen, bloating
- rapid increase in body weight
- swelling in any part of your body

Your doctor will give appropriate treatment for the fluid retention. If you have serious swelling your doctor may stop treatment until the swelling goes down.

*Low blood cell counts (platelets, red blood cells, and white blood cells)*
Low levels of certain blood cells (low blood cell counts) can be serious or severe. Your doctor or nurse will monitor your blood cell counts during treatment with ZYNLONTA. **Tell your healthcare professional immediately** if you have any signs and symptoms of infection. Low blood cell counts could be responsible for your infection.

*Skin reactions and exposure to sunlight*
Serious skin reactions have occurred in people treated with ZYNLONTA. Exposure to sunlight (including through glass or car windows) may cause severe sunburn. It is important to wear sunscreen and appropriate clothing to ensure you do not burn. **Tell your healthcare professional immediately** if you get new or worsening severe skin reactions, including:

- sensitivity to sunlight including sunburn-like reactions such as skin peeling and irritation following exposure to light
- itchy rash
- blistering of skin
- darker skin patches
- irritation, swelling, pain, and/or skin damage at the injection site

***Children and adolescents***

This medicine should not be given to children or young people under the age of 18. This is because ZYNLONTA has not been studied in this subgroup.

***Contraception (men and women)***

- Women of child-bearing potential must use effective contraception during treatment with ZYNLONTA, and for 10 months after the last dose.
- Men with partners of child-bearing potential must use effective contraception during treatment with ZYNLONTA, and for 7 months after the last dose.
- Talk to your healthcare professional about effective contraception.

***Pregnancy***

ZYNLONTA may harm your unborn baby. You should avoid getting pregnant if you are taking this medicine. **Tell your healthcare professional immediately** if you become pregnant or think that you are pregnant during treatment with ZYNLONTA. Your doctor may do a pregnancy test before starting treatment with ZYLONTA.

Male patients with female partners of reproductive potential, should use effective contraception during treatment with ZYNLONTA and for 7 months after the last dose.

***Breast-feeding***

Do not breast-feed during treatment, and for 3 months after the last dose. It is not known if ZYNLONTA passes into breast milk.

***Fertility***

ZYNLONTA may cause fertility problems in men, which may affect their ability to father children. You can seek advice on how to preserve sperm before starting treatment. Talk to your doctor for more information.

***Driving and using machines***

If you get infusion-related reactions or if you feel tired, weak or dizzy do not drive, cycle or use tools or machines until you feel better.

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

Interactions between ZYNLONTA and other drugs, vitamins, minerals, natural supplements or alternative medicines have not been established.

**How to take ZYNLONTA:**

- ZYNLONTA will be given to you by a healthcare professional experienced in cancer treatment, in a hospital or clinic. ZYNLONTA is given as a drip into a vein (intravenous infusion) over a period of 30 minutes.
- ZYNLONTA is usually given every 3 weeks (on day 1 of a 21-day cycle).
- Your healthcare professional may give you medicine before each infusion to decrease your chance of side effects.
- Your healthcare professional may stop your treatment, delay your treatment, or change your dose of ZYNLONTA if you have severe side effects.
- Your healthcare professional should do blood tests regularly to check for side effects of ZYNLONTA.
- Your healthcare professional will decide how many treatments you need.

**Usual dose:**

The dose of this medicine depends on your body weight. The usual starting dose is 0.15 mg for each kilogram (kg) of body weight.

The table below shows the recommended dose in each treatment cycle.

| **Recommended Dose** | ***Cycle*** |
|---|---|
| 0.15 mg per kg every 3 weeks | 1st Cycle |
| 0.15 mg per kg every 3 weeks | 2nd Cycle |
| 0.075 mg per kg every 3 weeks | 3rd Cycle onwards |

Your healthcare professional may lower your dose if you experience any serious side effects.

*Taking dexamethasone with ZYNLONTA*

During your treatment with ZYNLONTA you will also be given another medicine called dexamethasone to help reduce side effects as a result of treatment.

You will be given 4 mg of dexamethasone either by mouth or into your vein twice a day for three days, beginning the day before you receive ZYNLONTA treatment. If you do not receive dexamethasone the day before your treatment, then it must be given at least 2 hours before you are given ZYNLONTA.

**Overdose:**

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

**Missed Dose:**

If you miss an appointment to have ZYNLONTA administered, make another one straight away. For treatment to be fully effective, it is very important not to miss a dose. If you have any further questions on the use of this medicine, ask your healthcare professional.

**What are possible side effects from using ZYNLONTA?**

These are not all the possible side effects you may have when taking ZYNLONTA.

**Very common** (may affect more than 1 in 10 people):

- Loss of appetite
- Feeling sick or vomiting
- Cough
- Fever
- Diarrhea
- Stomach pain
- Constipation
- Reddening of the skin
- Rash
- Itching

**Common** (may affect up to 1 in 10 people):

- Nose and throat infection
- Rash characterized by a flat, red area on the skin that is covered with small, raised bumps
- Muscle pain
- Joint pain
- Back and neck pain
- Pain in the arms and legs
- Lack of energy

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **VERY COMMON** | | | |
| **Neutropenia** (low white blood cells called neutrophils): fever or infection, chills, fatigue, aches and pains, flu-like symptoms. | | x | |
| **Anemia** (low red blood cells): being short of breath, feeling very tired or cold, having pale skin, fast heartbeat, loss of energy, dizziness or weakness. | | x | |
| **Thrombocytopenia** (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, small purple dots (tiny bleeds) on your skin, fatigue, and weakness. | | x | |
| **Increased liver enzyme levels** (liver problems): symptoms may include skin and eyes appearing yellowish (jaundice), pain or discomfort in the upper right part of the abdomen, loss of appetite. | | x | |
| **Skin reactions:** sensitivity to sunlight, sunburn-like reactions such as skin peeling, redness or irritation following exposure to light, itchy rash, blistering of skin, darker skin patches, irritation, swelling, pain and/or skin damage at the injection site. | | x | |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **COMMON** | | | |
| **Infections:** fever, chills, flu-like symptoms (cough, tiredness or weakness, and body aches), severe headache; additional symptoms of lung infections including chest pain, shortness of breath, cough; additional symptoms of sepsis/septic shock including low blood pressure, cool, pale arms and legs, restlessness, agitation, lethargy or confusion. | | x | |
| **Fluid retention**: swelling in various parts of body including hands, feet, abdomen, or internal organs such as heart, lungs or abdomen, causing chest pain, difficulty breathing, abdominal pain or discomfort. | | x | |
| **Pneumonitis:** (inflammation of the lung tissue not caused by infection): shortness of breath, a dry cough that usually doesn't bring up any mucus. Symptoms may include extreme tiredness, loss of appetite, and fever. | | x | |
| **UNCOMMON** | | | |
| **Pericarditis** (inflammation around the heart): chest pain which may become worse when taking a deep breath, lie down, or swallow. Chest pain can be sharp or dull and may spread to shoulder and the upper back. Fever and dry cough may develop. | | x | |

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 healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

ZYNLONTA will be stored by the healthcare professional at the hospital or clinic where you are treated. The following information is intended for healthcare professionals.

Keep this medicine out of reach and sight of children.

Store in a refrigerator (2°C to 8°C). *Do not freeze*.

Keep the vial in the original carton in order to protect from light. Both the reconstituted solution and the diluted solution for infusion should not be frozen or exposed to direct sunlight.

ZYNLONTA is a cytotoxic medicine. Applicable special handling and disposal procedures must be followed.

Your healthcare professional is responsible for disposing of any unused ZYNLONTA correctly. These measures will help protect the environment.

**If you want more information about ZYNLONTA:**

- 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 (https://www.sobi.com/canada/en), or by calling 1-289-291-3852.

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