Zynlonta®
loncastuximab tesirine
for injection, for intravenous use • 10mg

ZYNLONTA▼
(loncastuximab tesirine)
Pharmacy Manual

Prescribing Information is available via the QR code or link on the inside back page

ZYNLONTA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.[1]

This medicinal product has been authorised under a 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

ZYNLONTA is a potent and selective single-agent CD19-targeted ADC therapy.[1,2]

This Pharmacy Manual has been designed to provide key information about ZYNLONTA.

SECTION 1:
Guidance for pharmacists:

- Product overview
- Indication & Pharmacology
- Preparation

SECTION 2:
Guidance for clinicians:

- Administration
- Safety overview
- Risk management protocols

Special warning: This product is cytotoxic. Applicable special handling and disposal procedures must be followed.[1]

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Swedish Orphan Biovitrum Ltd by email at medical.info.uk@sobi.com or by calling +44 (0) 800 111 4754.

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SECTION 1: Guidance for pharmacists

1.1 PRODUCT OVERVIEW: ZYNLONTA (loncastuximab tesirine)

1.1.1 Brand name

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loncastuximab tesirine
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1.1.2 Package description

1.1.2.1 Contents of pack carton

One single-use clear Type 1 glass vial, closed with a Teflon-coated rubber stopper and aluminum seal with plastic flip-off cap.

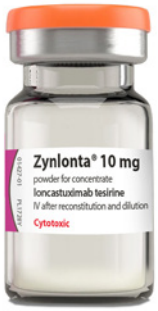
1.1.2.2 Carton dimensions

35 mm H x 62 mm W x 35 mm D.

1.1.2.3 Product expiration date

Printed on both single-dose vial and carton.

1.1.3 Storage & stability: Unopened vials



Store unopened vials in a refrigerator at 2–8°C.[1]

Shelf life: 5 years.[1]

Do not use beyond the expiration date on the carton or vial.[3]

Do not shake.[1]

Keep the vial in the outer carton to protect from light.[1]

1.1.4 General considerations for handling ZYNLONTA

- ZYNLONTA must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.[1]
- Follow procedures appropriate and applicable to cytotoxic and antineoplastic drugs when handling and disposing of ZYNLONTA.[1]
- **ZYNLONTA is for IV use after reconstitution and dilution.[1]**
- Prior to IV administration, ZYNLONTA must be reconstituted with 2.2 mL sterile water for injections and diluted into an **IV infusion bag containing 5% glucose. Follow proper aseptic technique throughout the preparation procedure** as the reconstituted product contains no preservative.[1]
- ZYNLONTA is intended for single use only.[1]
- Do not mix ZYNLONTA with – or administer as an infusion with – other drugs.[1]
- Do not freeze or expose the unopened vials, reconstituted solution, or diluted solution for injection to direct sunlight.[1]

1.1.5 Traceability

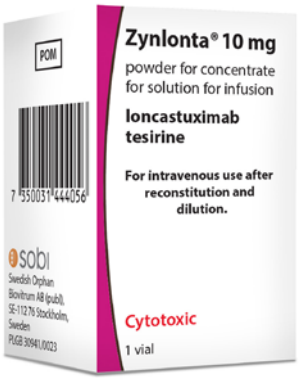
Clearly record the name and batch number of the administered ZYNLONTA product as per your pharmacy's guidelines to improve the traceability of biological medicinal products.[1]

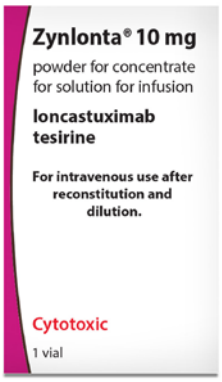
1.1.6 Distributor details for pharmacists

Email Address: allogauk.orders@alloga.co.uk

Telephone: + 44 (0)1773 441 702 | Fax: + 44 (0) 1773 810 644

Product code: APC2598





1.2 INDICATION & PHARMACOLOGY

1.2.1 Indication

ZYNLONTA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.[1]

Contraindications to use:

Hypersensitivity to the active substance or any of the excipients.[1]

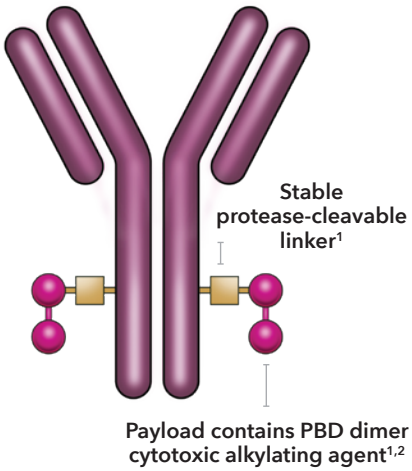
1.2.2 Clinical pharmacology

Pharmacotherapeutic group for ZYNLONTA: Antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX22.[1]

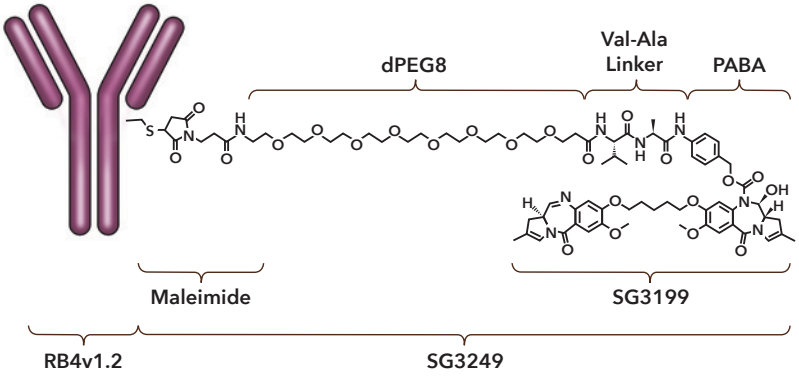
1.2.3 Molecular structure

Loncastuximab tesirine is a selective CD19-directed antibody drug conjugate (ADC) composed of a humanised IgG1 kappa monoclonal antibody (RB4v1.2) to which the cytotoxin SG3199 has been conjugated through a cathepsin-cleavable linker. The toxin SG3199 attached to the linker is designated as SG3249, also known as tesirine.[4]

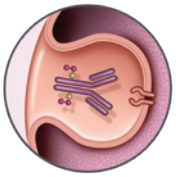
CD19-targeting humanised monoclonal antibody[1]



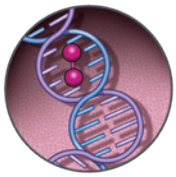
Loncastuximab tesirine molecular structure[2]



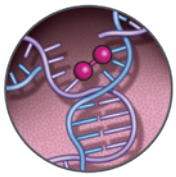
1.2.4 Mode of action



1. CD19 is a reliable marker for normal and neoplastic B-cells because it is expressed throughout B-cell maturation stages.[5]

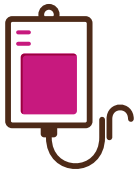


2. After binding to CD19 on the surface of B-cells in vivo, ZYNLONTA is internalised and the linker is cleaved, which releases free pyrrolobenzodiazepine (PBD) dimers (SG3199) into the target cell.[1,4]



3. The released SG3199 covalently binds to the minor groove of the target cell's DNA and forms highly cytotoxic DNA interstrand cross-links, which induces cell death.[1,3] As these cross-links are relatively non-distorting to the DNA structure, they are effectively hidden from the target cell's DNA repair mechanisms.[4]

1.2.5 Pharmacokinetics



The monoclonal antibody portion of the loncastuximab tesirine ADC is expected to be metabolised into small peptides by catabolic pathways, whereas the small molecule cytotoxin SG3199 is metabolised by CYP3A4/5 in vitro.[1]

Selected pharmacokinetic characteristics of loncastuximab tesirine at the approved recommended dosage are provided in the table below:[1]

PK parameter	In Cycle 1	In Cycle 2	At steady state
C_{max} (ng/mL)*	–	2795 (36.4%)	1705 (31.6%)
AUC_{tau} (ng • day/mL)*	–	22,082 (46.0%)	16,265 (34.9%)
$t_{½}$ (days) **	15.8 (6.26)	–	20.5 (5.72)

*Data presented as geometric mean and coefficient of variation (%CV)
**Data presented as mean (standard deviation)

Loncastuximab tesirine **C_{max} at steady state** was 39.0% lower than the **C_{max} after the second dose. The time to reach steady state was approximately 15 weeks**.[1] See *Dose calculation for ZYNLONTA*, section 1.3.3.

Of note, no clinically significant difference in the pharmacokinetics of loncastuximab tesirine has been observed based on age, sex, race, body weight, ECOG status, mild to moderate renal impairment, or mild hepatic impairment.[1]

Mild hepatic impairment may increase the exposure of unconjugated SG3199.[1]

1.2.6 Drug interactions

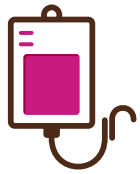
No studies in humans have examined the interactions between loncastuximab tesirine, free tesirine, SG3199, or related metabolites, and other medicinal products however, no clinically important PK interactions are expected.[1]

1.2.7 Immunogenicity

While there is a theoretical potential for an immune response in patients treated with therapeutic proteins like loncastuximab tesirine, no post-dose anti-drug antibodies were detected in patients treated with loncastuximab tesirine in the Phase 2 clinical registration trial (LOTIS-2).[1,6]

1.3 PREPARATION

1.3.1 Overview



ZYNLONTA is for IV use, administered over 30 minutes through 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.[1]

ZYNLONTA has not been studied with other administration routes.[1]

1.3.2 Qualitative and quantitative composition

1.3.2.1 Before reconstitution

Each single-use vial of ZYNLONTA contains **10 mg of loncastuximab tesirine** supplied as a sterile, white to off-white, lyophilized, preservative-free, cake-like powder for concentrate.[1,4]

Excipients consist of L-histidine, L-histidine monohydrochloride, polysorbate 20, and sucrose.[1]

1.3.2.2 After reconstitution

Each vial yields a single-use solution containing 5 mg/mL of loncastuximab tesirine in 20 mM histidine hydrochloride, 175 mM sucrose, and 0.02% w/v (0.2 mg/mL) polysorbate 20 at pH 6.[4]

1.3.3 Dose calculation for ZYNLONTA

It is important to initiate ZYNLONTA at the higher dose of 0.15 mg/kg for the first two Cycles, then adjust dosing to 0.075 mg/kg for subsequent Cycles.[1]

This regimen has been shown to deliver optimal response rates and duration of response in patients, while reducing cumulative toxicity.[7]

Single IV infusion  

The recommended dose of ZYNLONTA is 0.15 mg/kg every 21 days for 2 Cycles, followed by 0.075 mg/kg every 21 days for subsequent Cycles until disease progression or unacceptable toxicity.[1]

Cycle	Recommended dose[1]
Cycle 1	0.15 mg/kg every 21 days
Cycle 2	0.15 mg/kg every 21 days
Cycle 3 onwards	0.075 mg/kg every 21 days

Calculate the total dose (mg) required based on the patient's weight and prescribed dose.[1]

More than one vial may be needed to achieve the calculated dose.[1]

Convert the calculated dose (mg) to volume using 5 mg/mL, which is the concentration of ZYNLONTA after reconstitution.[1]

The table below provides a dose calculation **(EXAMPLE ONLY)** for a patient weighing 70 kg:

Dose Preparation Calculation Example with Intermediate Dilution for Low Doses	
Body weight	70 kg
Dose level	0.15 mg/kg
Concentration of reconstituted solution / concentration of intermediate dilution	5 mg/mL
Drug dose	10.5 mg
Final reconstitution into IV bag	50 mL
Total volume needed	10.5 mg / 5 mg/mL = 2.1 mL
Vials needed	2 vials (10 mg per vial)
Rounding (if required)	No rounding. Measure and deliver 2.1 mL in a 3 mL syringe

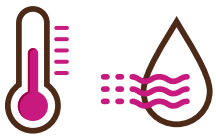
1.3.4 Density and reconstitution of powder for concentrate

ZYNLONTA is supplied as a sterile, preservative-free, lyophilized powder in a single-dose vial for reconstitution and further dilution.[1] The concentration range that has been demonstrated to be compatible in IV bags is 20 ug/mL to 500 ug/mL.

1.3.4.1 Reconstitution procedure

- Using a sterile syringe, slowly inject 2.2 mL of sterile water for injections against the inside wall of the vial containing ZYNLONTA 10 mg lyophilised powder to obtain a final concentration of 5 mg/mL.[1]
- **Do not mix ZYNLONTA with any other medicinal products.[1]**
- Gently swirl the vial until the powder has completely dissolved. **Do not shake the vial**.[1]
- The fully reconstituted solution should appear clear to slightly opalescent and colourless to slightly yellow.[1]
- **Do not use the product if the reconstituted solution contains visible particulates or appears discoloured or cloudy.[1]**
- **After reconstitution, each vial delivers up to 2 mL at a concentration of 5 mg/mL.**

1.3.4.2 Storage & stability: Reconstituted solution



The reconstituted solution contains no preservative and should be used immediately.[1]

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user but should not be longer than 4h refrigerated (2–8°C) or 4h room temperature (20–25°C) after reconstitution, unless reconstitution has taken place in controlled and validated aseptic conditions.[1]

Do not freeze the reconstituted solution.[1]

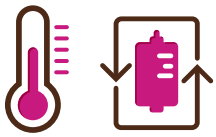
Discard any unused or expired product in accordance with your local protocols for disposal of cytotoxic medicines.[1]

1.3.5 Dilution in IV infusion bag

1.3.5.1 Dilution procedure

- **Using a sterile syringe, transfer the calculated dose volume of reconstituted solution from the vial to a 50 mL IV infusion bag containing 5% glucose.[1]**
- Gently mix the IV infusion bag by slowly inverting. **Do not shake the bag.[1]**
- Of note: No incompatibilities have been observed between ZYNLONTA and IV infusion bags with product-contacting materials of polyvinylchloride (PVC), polyolefin (PO), and PAB (copolymer of ethylene and propylene).[1]
- Discard any unused solution remaining in the vial in accordance with your local protocols for disposal of cytotoxic medicines.[1]

1.3.5.2 Prepared solution for infusion



The prepared solution for infusion contains no preservative and should be used immediately.[1]

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user but should not be longer than 24h refrigerated (2–8°C) or 8h room temperature (20–25°C) after reconstitution, unless reconstitution has taken place in controlled and validated aseptic conditions.[1]

Do not freeze the prepared solution for infusion.[1]

Discard any unused or expired product in accordance with your local protocols for disposal of cytotoxic medicines.[1]

2.1 ADMINISTRATION TO PATIENT

2.1.1 Pre-administration checklist

☑ **Please check the SPC for ZYNLONTA for dose modifications for treatment-related toxicity and warnings and precautions for use.**

☑ All patients have been advised to minimise or avoid exposure to direct natural or artificial sunlight during treatment, including exposure through windows, and instructed to protect their skin by wearing sun-protective clothing and/or sunscreen products.[1]

☑ All patients have been provided with a Patient Card as per the Risk Minimisation Measures to address the risk of phototoxicity.[1,4]

2.1.2 Dose modification protocols

2.1.2.1 Delayed or missed doses

Administer delayed or missed doses of ZYNLONTA as soon as possible.[1] Adjust the patient's administration schedule to maintain a 21-day interval between doses.[1]

2.1.2.2 Toxicity-related dose modifications

Consult the table below for recommended dose modifications in the event of ZYNLONTA-related adverse reactions:[1]

Adverse reactions	Severity	Dose modification
Haematologic adverse reactions		
Neutropenia	Absolute neutrophil count <1 x 10^9/L	Withhold ZYNLONTA until neutrophil count returns to ≥1 x 10^9/L
Thrombocytopenia	Platelet count <50,000/mcL	Withhold ZYNLONTA until platelet count returns to ≥50,000/mcL
Non-haematologic adverse reactions		
Oedema or effusion	Grade ≥2	Withhold ZYNLONTA until toxicity resolves to Grade ≤1
Other adverse reactions	Grade ≥3	Withhold ZYNLONTA until toxicity resolves to Grade ≤1

Reduce subsequent doses by 50% if a scheduled dose is delayed by more than 3 weeks due to ZYNLONTA-related toxicity.[1]

If toxicity requires a dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the recommended dose of 0.075 mg/kg for Cycle 3.[1]

Consider permanent treatment discontinuation if toxicity re-occurs after two dose reductions following an adverse reaction.[1]

2.1.2.3 Overdose

Initiate symptomatic treatment and standard supportive care measures to manage any observed toxicity as per your local institution's policies and guidelines.[1]

2.1.2.4 Dose adjustments for special patient populations

A. Overview

The pharmacokinetics of loncastuximab tesirine are not significantly affected by age, sex, race, body weight, ECOG status, mild to moderate renal impairment, or mild hepatic impairment.[1]

B. BMI ≥35 kg/m^2

No specific requirements are needed on adjusting dose for patient BMI.[1]

C. Elderly (≥65 years of age)

No dose adjustment is required.[1] In the Phase 2 clinical trial (LOTIS-2), no overall differences in the safety or effectiveness of ZYNLONTA were observed between patients aged <65 years (n=65/145) and patients aged ≥65 years (n=80/145).[6]

D. Paediatric (<18 years of age)

ZYNLONTA is not indicated for use in patients aged <18 years.[1] The safety and efficacy of ZYNLONTA in patients aged <18 years have not been established and no data are available.[1]

E. Patients of childbearing potential

ZYNLONTA is not recommended in women of childbearing potential who are not using contraception.[1] Female patients of childbearing potential and male patients with partners of childbearing potential should use effective contraception during treatment with ZYNLONTA and for a specified period thereafter; see sections 2.1.1, 2.3.6, 2.3.7 and 2.3.8 for more information.

F. Renal impairment

Mild to moderate renal impairment (CLcr 30 to 90 mL/min): No dose adjustment is required.[1] Clearance of loncastuximab tesirine in patients with mild to moderate renal impairment was not significantly different from patients with normal renal function.[1] There is no clinical data for the toxin SG3199 component of ZYNLONTA, however data collected in a rat model showed minimal renal excretion.[1]

Severe renal impairment (CLcr 15 to 29 mL/min): No data available.[1] ZYNLONTA has not been studied in this patient group, and the effects of severe renal impairment and ESRD (with or without haemodialysis) on the pharmacokinetics of ZYNLONTA is unknown.[1] Additional monitoring for adverse reactions may be warranted if ZYNLONTA is administered to these patients.[1]

G. Hepatic impairment

Monitoring for adverse reactions is recommended in all patients with hepatic impairment.[1]

Mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 × ULN and any AST): No dose adjustment is required.[1] Mild hepatic impairment may increase the exposure of unconjugated SG3199 but has no clinically significant effect on the pharmacokinetics of loncastuximab tesirine.[1]

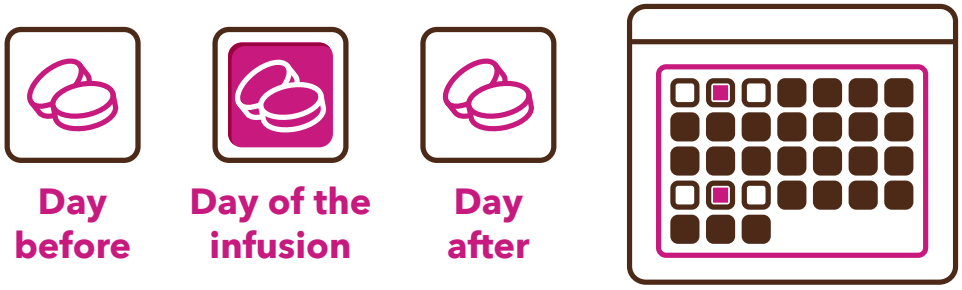
Moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and any AST): No data available.[1]
ZYNLONTA has not been studied in this patient group.[1]

2.1.3 Premedication with dexamethasone

2.1.3.1 Rationale:

Unless contraindicated, premedication with dexamethasone is recommended to mitigate PBD-associated toxicities.[1]

2.1.3.2 Dexamethasone administration schedule



Beginning the day before administering ZYNLONTA, administer oral or IV dexamethasone 4 mg twice daily for 3 days.[1]

If dexamethasone administration does not begin the day before ZYNLONTA, it should begin **at least 2 hours** before administering the infusion.[1]

2.1.4 Infusion procedure

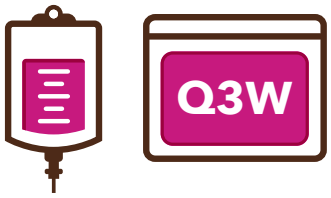
ZYNLONTA single agent therapy can be administered in an in-patient or out-patient setting.

ZYNLONTA must only be administered under the supervision of a healthcare professional who is experienced in the diagnosis and treatment of cancer patients.[1]

Each ZYNLONTA infusion should be administered over 30 minutes through 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.[1]

ZYNLONTA is for single-use dosing only.[1]

Single IV infusion once every 3 weeks



30-minute infusion time

Do not mix ZYNLONTA with – or administer as an infusion with – any medicinal products other than those specified in this Pharmacy Manual, which is aligned to the ZYNLONTA SPC.[1]

2.1.5 Extravasation

Extravasation of ZYNLONTA has been associated with irritation, swelling, pain, and/or tissue damage, which may be severe.[1]

Monitor the infusion site for possible SC infiltration during administration.[1]

Advise patients to immediately report any changes in sensation, stinging, or burning during the infusion process, as well as any infusion site symptoms that develop after drug administration.[1,8]

Initiate appropriate management of extravasation as per your local institution's recommended guidelines as soon as it is suspected.[8]

Following each infusion of ZYNLONTA, discard any unused or expired product in accordance with your local protocols for disposal of cytotoxic medicines.[1]

2.2 SAFETY OVERVIEW

2.2.1 Summary of the safety profile

Data for adverse reactions derives from 215 patients with r/r DLBCL who received ZYNLONTA as single-use infusion at the recommended dose for a median of 45 days (range 1–569 days) in two clinical trials (Phase 2 LOTIS-2, N=145; and Phase 1 LOTIS-1, N=70).[1]

The most frequent adverse reactions with ZYNLONTA are provided in the tables below (N=215):[1]

2.2.1.1 Overall adverse reactions

35.8%	γ-glutamyltransferase (GGT) increased
34.9%	Neutropenia
30.2%	Fatigue
28.8%	Anaemia
28.4%	Thrombocytopenia
26.5%	Nausea
23.3%	Peripheral oedema
20.0%	Rash

2.2.1.2 Severe (≥Grade 3) adverse reactions

24.2%	Neutropenia
17.2%	γ-glutamyltransferase (GGT) increased
15.8%	Thrombocytopenia
11.6%	Anaemia
9.8%	Infections

2.2.1.3 Adverse reactions leading to dose modification

A. Dose reduction

3.3%	γ-glutamyltransferase (GGT) increased

B. Dose delay

17.7%	γ-glutamyltransferase (GGT) increased
11.2%	Neutropenia
7.9%	Thrombocytopenia

2.2.1.4 Adverse reactions leading to treatment withdrawal

8.8%	γ-glutamyltransferase (GGT) increased
2.8%	Peripheral oedema
1.9%	Thrombocytopenia
1.4%	Pleural effusion
1.4%	Pericardial effusion

The full safety profile for ZYNLONTA is available at:

https://www.medicines.org.uk/emc/product/14786/smpc#gref

2.3 RISK MANAGEMENT PROTOCOLS

▼**This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Swedish Orphan Biovitrum Ltd by email at medical.info.uk@sobi.com or by calling +44 (0) 800 111 4754.**

ZYNLONTA must only be administered under the supervision of a healthcare professional who is experienced in the diagnosis and treatment of cancer patients.[1]

2.3.1 Effusion and oedema

2.3.1.1 Description

Serious cases of effusions and oedema have been reported during treatment with ZYNLONTA.[1,3]

In clinical trials (LOTIS-1 and LOTIS-2), the median time to onset of Grade ≥3 effusions and oedema was 115 days and 101 days, respectively.[1]

2.3.1.2 Management

- **Monitor patients for new or worsening effusions or oedema.**[1,3,4]
- **Withhold ZYNLONTA in the event of Grade ≥2 effusions or oedema,** until the toxicity resolves to Grade 1 or less.[1,3,4]
- Instruct patients to inform their doctor if they develop symptoms of fluid retention such as chest pain, difficulty breathing, or swelling in any part of their body.[3,4]
- Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnoea, chest pain, and/or ascites such as swelling in the abdomen and bloating.[1]
- Initiate appropriate medical management for effusions or oedema as directed by your local institution's policies and guidelines.[1]

2.3.2 Myelosuppression

2.3.2.1 Description

Serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anaemia, can occur during treatment with ZYNLONTA.[1]

In clinical trials (LOTIS-1 and LOTIS-2), the median time to onset for Grade 3/4 neutropenia, thrombocytopenia, and anaemia was 36.0 days, 28.5 days, and 22.0 days, respectively.[1]

2.3.2.2 Management

- **Monitor complete blood cell counts** prior to each dose of ZYNLONTA.[1]
- **Withhold ZYNLONTA if absolute neutrophil count is less than 1x10^9/L,** until it returns to 1x10^9/L or higher.[1]
- **Withhold ZYNLONTA if platelet count is less than 50,000/mcL,** until it returns to 50,000/mcL or higher.[1]
- Cytopenias may require more frequent lab monitoring and/or dose interruption, dose reduction, or discontinuation of ZYNLONTA.[1]
- Consider prophylactic use of granulocyte colony-stimulating factor, if appropriate.[1]

2.3.3 Infections

2.3.3.1 Description

Fatal and serious infections, including opportunistic infections and sepsis, have been reported in patients treated with ZYNLONTA.[1]

2.3.3.2 Management

- **Monitor patients for any new or worsening signs or symptoms consistent with infection,**[1] such as but not limited to: fever, chills, flu-like symptoms (cough, tiredness, weakness, body aches, etc.), severe headache, or cuts/scrapes that are red, warm, swollen, or painful.[3]
- **Withhold ZYNLONTA in the event of Grade 3 or 4 infection,** until it has resolved to Grade 1 or less.[1]
- Instruct patients to inform their doctor if they develop symptoms of active infection, or notice bruising or bleeding, during treatment with ZYNLONTA.[1,3]

2.3.4 Photosensitivity and cutaneous reactions

2.3.4.1 Description

Treatment with ZYNLONTA has been associated with severe (Grade 3) cutaneous reactions, photosensitivity reactions, rash, rash pustular, rash maculo-papular, and erythema.[1]

In clinical trials (LOTIS-1 and LOTIS-2), the median time to onset for Grade 3 photosensitivity reactions and Grade 3 non-photosensitivity cutaneous reactions was 32.0 days and 56.0 days, respectively.[1]

2.3.4.2 Management

- **Monitor patients for new or worsening cutaneous reactions,** including photosensitivity reactions.[1,4]
- **Withhold ZYNLONTA in the event of any severe (Grade 3) cutaneous reaction**, until it has resolved to Grade 1 or less.[1,4]
- Oral and topical corticosteroids and anti-pruritic therapy were used in clinical trials (LOTIS-1 and LOTIS-2) to treat cutaneous reactions.[1]
- Consider dermatologic consultation if a skin reaction or rash develops during treatment.[1,4]
- Advise patients to minimise or avoid exposure to direct natural or artificial sunlight, including exposure through glass or car windows, and instruct patients to protect skin by wearing sun-protective clothing and/or sunscreen products.[1,3,4]
- Instruct patients to inform their doctor if they notice new or worsening severe skin reactions, such as, but not limited to: Sensitivity to sunlight including sunburn-like reactions such as skin peeling and irritation following exposure to light, itchy rash, skin blistering, darker skin patches, irritation, swelling, pain, and/or skin damage at the ZYNLONTA infusion site.[3,4]

2.3.4.3 Risk minimisation material (RMM) for phototoxicity (Patient Card)

- The RMM Patient Card should be carried at all times by patients receiving treatment with ZYNLONTA for r/r DLBCL or HGBL.[1]
- The RMM Patient Card provides patients with the following key safety information:
  - Treatment with ZYNLONTA may increase the risk of photosensitivity reactions.[1]
  - Signs and symptoms of photosensitivity reactions.[1]
  - Instructions to avoid exposure to direct/indirect sunlight, and to contact a healthcare professional if any skin eruption occurs.[1]

2.3.5 Liver function

2.3.5.1 Description

Abnormal liver function tests of severity Grade ≥3 occurred in 19.5% of 215 patients in clinical trials for ZYNLONTA (LOTIS-1 and LOTIS-2), which occasionally necessitated dose delays, dose reductions and treatment withdrawal in affected patients.[1]

Parameters affected included increased γ-glutamyltransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, increased aspartate aminotransferase, and increased blood bilirubin.[1]

2.3.5.2 Management

- **Monitor complete liver function tests** prior to each dose of ZYNLONTA.[1]
- **Withhold ZYNLONTA in the event of Grade 3 or 4 liver function test,** until it has resolved to Grade 1 or less.[1]
- Advise patients to inform their doctor if they have liver problems or notice any symptoms of skin and eyes appearing yellowish (jaundice).[3]

2.3.6 Embryo-foetal toxicity & pregnancy

2.3.6.1 Description

ZYNLONTA contains SG3199, a genotoxic compound that affects actively dividing cells and could therefore cause embryo-foetal harm if administered to a pregnant woman.[1]

There are no data on the use of ZYNLONTA in pregnant women, and treatment is not recommended in patients of childbearing potential who are not using effective contraception.[1]

2.3.6.2 Management

- **Test for pregnancy** in female patients of childbearing potential prior to initiating ZYNLONTA, and prior to each subsequent treatment infusion.[1,4]
- Do not recommend treatment with ZYNLONTA during pregnancy unless the potential benefit for the pregnant patient outweighs the potential risk to the foetus.[4]
- Advise pregnant patients of the potential genotoxic risk to the foetus.[1,4]
- **Advise female patients of childbearing potential to use effective contraception** during treatment with ZYNLONTA and for 10 months after the last dose, and to speak with their doctor if they are planning to become pregnant.[1,3,4]
- Advise female patients of childbearing potential to inform their doctor immediately if they become pregnant either during or following treatment with ZYNLONTA.[3,4]
- **Advise male patients with partners of childbearing potential to use effective contraception** during treatment with ZYNLONTA and for 7 months after the last dose.[1,3,4]

2.3.7 Breastfeeding

2.3.7.1 Description

There are no data on the presence of loncastuximab tesirine or SG3199 in human milk, the effects on the breastfed child, or milk production.[1] It is not known if ZYNLONTA passes into breast milk, so a risk for breast-fed children cannot be excluded.[1,3]

2.3.7.2 Management

- **Advise female patients to discontinue breastfeeding during treatment with ZYNLONTA** and for at least 3 months after the last dose.[1,3]

2.3.8 Male fertility

2.3.8.1 Description

ZYNLONTA may impair male fertility.[1,3] Fertility studies have not been undertaken with loncastuximab tesirine in humans however, repeat-dose toxicity studies in a cynomolgus monkey model resulted in testicular toxicity.[1]

2.3.8.2 Management

- **Advise male patients to consider preserving and storing sperm samples** before initiating treatment with ZYNLONTA.[1,3]

Abbreviations

ADC, antibody drug conjugate; **AST**, aspartate aminotransferase; **ATC**, Anatomical Therapeutic Chemical; **AUC_{tau}**, area under the curve over the dosing interval; **BMI**, body mass index; **CLcr**, creatinine clearance; **C_{max}**, maximum predicted serum concentration; **CYP3A4/5**, cytochrome P450 3A4/3A5; **DLBCL**, diffuse large B-cell lymphoma; **DNA**, deoxyribonucleic acid; **ECOG**, Eastern Cooperative Oncology Group; **ESRD**, end-stage renal disease; **HGBL**, high-grade B-cell lymphoma; **IgG1**, immunoglobulin G 1; **IV**, intravenous; **PBD**, pyrrolobenzodiazepine; **PK**, pharmacokinetic; **R/R**, relapsed/refractory; **SC**, subcutaneous; **SPC/SmPC**, summary of product characteristics; **$t_{½}$**, half-life; **ULN**, upper limit of normal

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