▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ZYNLONTA (LONCASTUXIMAB TESIRINE)

1 NAME OF THE MEDICINE

Loncastuximab tesirine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for concentrate for solution for infusion contains 10 mg of loncastuximab tesirine. After reconstitution, each vial contains 5 mg/mL of loncastuximab tesirine.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ZYNLONTA is a powder for concentrate for solution for infusion (powder for infusion after preparation).

ZYNLONTA is a white to off-white lyophilised powder, which has a cake-like appearance.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZYNLONTA monotherapy is provisionally approved for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy.

ZYNLONTA is not indicated for patients with primary central nervous system lymphoma.

The decision to approve this indication has been granted on the results from an open-label, uncontrolled Phase 2 study based on the overall response rate. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dose

The recommended dose of ZYNLONTA is 0.15 mg/kg every 3 weeks for first 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 an adjusted body weight (ABW) as follows:

- ABW in kg = 35 kg/m^2 × (height in meters)^2

Premedication with dexamethasone

Unless contraindicated, dexamethasone 4 mg is to be administered orally or intravenously twice daily for 3 days, beginning the day before administering ZYNLONTA to mitigate pyrrolobenzodiazepine (PBD)-related toxicities. If dexamethasone administration does not begin the day before ZYNLONTA, oral or intravenous dexamethasone should begin at least 2 hours prior to administration of ZYNLONTA.

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 21day interval between doses.

Dose modifications

For dose modification for haematologic and non-haematologic adverse reactions (see section 4.8 Adverse effects (Undesirable effects)), see Table 1 below.

Table 1: ZYNLONTA dose modification for haematologic and non-haematologic adverse reactions

Adverse reactions	Severity	Dose modification
Haematologic 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/microlitre	Withhold ZYNLONTA until platelet count returns to 50,000/microlitre or higher
Non-haematologic adverse reactions		
Oedema or effusion	Grade 2 or higher	Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less
Hepatotoxicity,	Grade 3 or higher increase in bilirubin, AST, ALT, GGT and/or ALP.	Withhold ZYNLONTA until toxicity resolves to Grade 1 or less.
Other adverse reactions	Grade 3 or higher	Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less

If dosing is delayed by more than 3 weeks due to toxicity related to ZYNLONTA, subsequent doses should be reduced by 50%.

If toxicity occurs 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 and subsequent cycles.

If toxicity reoccurs after two dose reductions following an adverse reaction, permanent discontinuation of Zynlonta should be considered.

Special populations

Elderly

No dose adjustment of ZYNLONTA is required in patients ≥65 years of age (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

Renal impairment

No dose adjustment of ZYNLONTA is required for patients with mild to moderate renal impairment (see section 5.2 Pharmacokinetic properties). ZYNLONTA has not been studied in patients with severe renal impairment (CrCl 15 to 29 mL/min) (see section 4.4 Special warnings and precautions for use).

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 section 5.2 Pharmacokinetic properties).

ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) (see section 4.4 Special warnings and precautions for use).

Paediatric population

The safety and efficacy of loncastuximab tesirine in children and adolescents aged less than 18 years have not been established.

Preparation and Administration

ZYNLONTA is for intravenous use.

The infusion is administered over 30 minutes through an intravenous line.

Extravasation of ZYNLONTA has been associated with irritation, swelling, pain, and/or tissue damage, which may be severe (see section 4.8 Adverse effects (Undesirable effects)). The infusion site should be monitored for possible subcutaneous infiltration during medicinal product administration.

ZYNLONTA contains a cytotoxic component and should be administered under the supervision of a healthcare professional experienced in the use of cytotoxic agents. Procedures for proper handling and disposal of antineoplastic and cytotoxic medicinal products should be used.

ZYNLONTA must be reconstituted and diluted using aseptic technique under the supervision of a healthcare professional. It must be administered 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 micrometre pore size) and catheter.

ZYNLONTA must be reconstituted using sterile water for injections and diluted into an intravenous infusion bag containing 5% glucose prior to administration.

Dose calculation

Calculate the total dose (mg) required based on the patient's weight and prescribed dose. More than one vial may be needed to achieve the calculated dose.

Reconstitution of powder for concentrate

- Reconstitute each vial of powder for concentrate using 2.2 mL of sterile water for injections 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. More than

one vial may be needed to achieve the calculated dose.

- Inspect the reconstituted solution for particulate matter and discolouration. The solution should appear clear to slightly opalescent, colourless to slightly yellow. Do not use if the reconstituted solution is discoloured, is cloudy, or contains visible particulates.
- Discard unused vial after reconstitution if the recommended storage time is exceeded.

The reconstituted solution should be used immediately (refer 6.4 Special precautions for storage).

Dilution in intravenous infusion bag

- Withdraw the required volume of reconstituted solution from the vial using a sterile syringe. Discard any unused portion left in the vial.
- Add the calculated dose volume of ZYNLONTA reconstituted solution into a 50 mL intravenous infusion bag of **5% glucose**.
- Gently mix the intravenous infusion bag by slowly inverting the bag. **Do not shake**.
- 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).
- ZYNLONTA must be administered 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 micrometre pore size) and catheter.

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 (refer Section 6.4 Special precautions for storage).

Both the reconstituted solution and the diluted solution for infusion should not be frozen or exposed to direct sunlight.

The powder for concentrate, the reconstituted solution and the diluted solution contains no preservative and is intended for single use in one patient on one occasion only. Discard any unused portion left in the vial or infusion bag.

4.3 CONTRAINDICATIONS

Known hypersensitivity to loncastuximab tesirine or to any of the inactive ingredients (see section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Effusion and oedema

Serious effusion and oedema have been reported in patients treated with ZYNLONTA (see section 4.8 Adverse effects (Undesirable effects)). In clinical study ADCT-402-201 (LOTIS-2), these events were numerically more frequent in patients with pre-existing cardiac or renal disease than in those without. However, given the potential for confounding and due to small subgroup size, these differences should be interpreted cautiously.

Patients should be monitored for new or worsening oedema or effusions, including weight gain

without another explanation. ZYNLONTA should be withheld for Grade 2 or greater oedema or effusion until the toxicity resolves (see section 4.2 Dose and method of administration). Diagnostic imaging should be considered 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. Appropriate medical management for oedema or effusions should be instituted.

In patients with worsening effusion or oedema, who have signs and symptoms of weight gain, severe hypotension, hypoalbuminemia, and/or haemoconcentration (by elevated haemoglobin/haematocrit, etc.), capillary leak syndrome should be considered and appropriate medical management instituted.

Myelosuppression

Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anaemia (see section 4.8 Adverse effects (Undesirable effects)).

Complete blood cell counts should be monitored prior to each dose of ZYNLONTA. Cytopenia may require more frequent lab monitoring and/or interruption, dose reduction, or discontinuation of ZYNLONTA. Prophylactic granulocyte colony-stimulating factor administration should be considered, as applicable (see section 4.2 Dose and method of administration).

Infections

Fatal and serious infections, including opportunistic infections and sepsis, have been reported in patients treated with ZYNLONTA (see section 4.8 Adverse effects (Undesirable effects)).

Patients should be monitored for any new or worsening signs or symptoms consistent with infection.

Hepatotoxicity

Grade ≥3 increase in liver function tests, including severe liver injury, have been reported in patients treated with ZYNLONTA (see section 4.8 Adverse effects (Undesirable effects)). Liver function tests should be monitored at baseline and throughout treatment with ZYNLONTA. In the event of a Grade ≥3 increase in alanine aminotransferase (ALT) or AST, ZYNLONTA should be withheld until toxicity resolves to Grade 1 or lower (see section 4.2 Dose and method of administration).

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

Photosensitivity and cutaneous reactions

Serious cutaneous reactions have been reported in patients treated with ZYNLONTA.

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 section 4.2 Dose and method of administration). Patients should be advised to minimise 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.

Embryofetal toxicity

ZYNLONTA may cause embryofetal 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.

Women of childbearing potential should be advised to use effective contraception during treatment with ZYNLONTA and for 10 months after the last dose. Men with partners of childbearing potential should be advised to use effective contraception during treatment with ZYNLONTA, and for 7 months after the last dose (see section 4.6 Fertility, pregnancy and lactation).

Fertility

Male patients should be advised to consider preservation of sperm prior to treatment with loncastuximab tesirine. Studies in animals have been reported to result in testicular toxicity (atrophy with reduced spermatogenesis), which had not reversed after a 12-week treatment-free period.

Use in renal impairment

No dose adjustment of ZYNLONTA is required for patients with mild to moderate renal impairment (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetics in Special Populations). ZYNLONTA has not been studied in patients with severe renal impairment (CrCl 15 to 29 mL/min).

Use in the elderly

No dose adjustment of ZYNLONTA is required in patients ≥65 years of age (See section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties).

Paediatric use

The safety and efficacy of ZYNLONTA in children and adolescents aged less than 18 years have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed in humans for loncastuximab tesirine, free tesirine, SG3199 and related metabolites.

In vitro studies

SG3199 does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 at clinically relevant unconjugated SG3199 concentrations. SG3199 is not a clinically relevant inducer of CYP1A2, CYP2B6 or CYP3A4.

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, OATP1B3, or organic cation transporter (OCT)1.

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) at clinically relevant unconjugated SG3199 concentrations.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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 once every 3 weeks at ≥0.075mg/kg resulted in minimal to severe 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 at ≥0.15 mg/kg. No reduced epididymis sperm count was seen at 0.075 mg/kg. The dose of 0.075 mg/kg in animals resulted in an exposure (AUC) that is approximately 0.7 times the exposure at the maximum recommended human dose [MRHD] of 0.15 mg/kg. Findings were not reversible at the end of a 12 week recovery period following 4 or 13 weeks of dosing.

Based on the results from animal studies, loncastuximab tesirine may impair male fertility. Therefore, men being treated with this medicine should be advised to consider having sperm samples preserved and stored before initiating treatment.

Use in pregnancy – Pregnancy (Category D)

There are no data on the use of loncastuximab tesirine during pregnancy. No animal embryofetal development studies were conducted with loncastuximab tesirine. ZYNLONTA may cause embryofetal toxicity when administered during pregnancy, because it contains a genotoxic compound (SG3199) that affects actively dividing cells. Furthermore, loncastuximab tesirine may be expected to cross the placenta in the third trimester. ZYNLONTA is not recommended during pregnancy unless the potential benefit for the woman outweighs the potential risk to the fetus..

Pregnancy testing is advised for women of childbearing potential prior to initiating ZYNLONTA.

Contraception in men and women

Women: Women of childbearing potential should be advised to use effective contraception during treatment with loncastuximab tesirine and for at least 10 months after the last dose.

Men: Because of the potential for genotoxicity, men with partners of childbearing potential should be advised to use effective contraception during treatment with loncastuximab tesirine and for at least 7 months after the last dose.

Use in lactation

There is no data on the presence of loncastuximab tesirine or SG3199 in human milk, the effects on the breastfed child, or milk production. A risk for breast-feeding children cannot be excluded. Breastfeeding should be discontinued during treatment with ZYNLONTA and for at least 3 months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ZYNLONTA has no or negligible influence on the ability to drive and use machines. However, fatigue has been reported in patients taking loncastuximab tesirine and this should be taken into account when driving or using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of loncastuximab tesirine was evaluated in the pivotal phase II study (see Section 5.1 Clinical trials). A total of 145 patients received 150 µg/kg loncastuximab tesirine monotherapy every 3 weeks for 2 cycles followed by 75 µg/kg every 3 weeks for subsequent cycle were included in the safety analysis. 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.

Summary of the safety profile

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

The most frequent (≥2%) serious adverse reactions were hypercalcaemia (4.1%), 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 most common adverse reaction leading to dose reductions was GGT increased reported in 5 patients (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 oedema (2.8%), localised oedema (2.1%), and pleural effusion (2.1%).

Tabulated list of adverse reactions

Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies in the clinical study ADCT-402-201 (LOTIS-2), where a proportion of the events for an adverse reaction may have other causes than the medicinal product, such as the disease, other medicinal products or unrelated causes.

Table 2: Adverse events reported in at least 10% of patients with relapsed or refractory DLBCL treated with ZYNLONTA in LOTIS-2

	Loncastuximab tesirine N=145			
Primary System Organ Class Preferred Term*	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
General disorders and administration site conditions				
Fatigue	40 (27.6)	2 (1.4)	0	0
Oedema peripheral	29 (20.0)	2 (1.4)	0	0
Pyrexia	28 (19.3)	2 (1.4)	0	0
Blood and lymphatic system disorders				
Neutropenia	58 (40.0)	14 (9.7)	24 (16.6)	0
Thrombocytopenia	48 (33.1)	18 (12.4)	8 (5.5)	0
Anaemia	38 (26.2)	15 (10.3)	0	0
Leukopenia	21 (14.5)	9 (6.2)	4 (2.8)	0
Investigations				
Gamma-glutamyltransferase increased	61 (42.1)	23 (15.9)	2 (1.4)	0
Blood alkaline phosphatase increased	29 (20.0)	1 (0.7)	0	0
Alanine aminotransferase increased	22(15.2)	4 (2.8)	0	0
Aspartate aminotransferase increased	23 (15.9)	1 (0.7)	0	0
Gastrointestinal disorders				
Nausea	34 (23.4)	0	0	0
Diarrhoea	25 (17.2)	3 (2.1)	0	0
Vomiting	19 (13.1)	0	0	0
Abdominal pain	17 (11.7)	3 (2.1)	1 (0.7)	0
Constipation	17 (11.7)	0	0	0
Metabolism and nutrition disorders				
Hypophosphataemia	23 (15.9)	7 (4.8)	1 (0.7)	0
Hypokalaemia	23(15.9)	6 (4.1)	0	0
Decreased appetite	22 (15.2)	0	0	0
Hypomagnesaemia	20 (13.8)	1 (0.7)	0	0
Skin and subcutaneous tissue disorders				
Rash	19 (13.1)	1 (0.7)	0	0
Pruritus	19 (13.1)	0	0	0
Photosensitivity reaction	15 (10.3)	3 (2.1)	0	0
Erythema	15 (10.3)	1 (0.7)	0	0
Respiratory, thoracic and mediastinal disorders				
Cough	33(22.8)	1 (0.7)	0	0
Dyspnoea	17 (11.7)	2 (1.4)	0	0
Pleural effusion	16 (11.0)	3 (2.1)	0	0
Psychiatric disorders				
Insomnia	16 (11.0)	0	0	0
Nervous system disorders				
Headache	15 (10.3)	1 (0.7)	0	0

* Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0.
n - Number of patients

Description of Selected Adverse Reactions (LOTIS-2)

Effusion or Oedema

Serious effusion and oedema occurred in patients treated with ZYNLONTA. Grade ≥3 oedema 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 oedema occurred in 2.1%, 2.1% and 1.4% of patients, respectively

Fatigue

Fatigue of severity Grade 3 occurred in 2.1% of patients treated with ZYNLONTA, including fatigue occurring in 1.4% of patients and malaise noted in 0.7% of patients.

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.

Liver function test abnormalities

Abnormal liver function tests of severity Grade ≥3 occurred in 20.7% of patients, with Grade 3 or 4 gamma-glutamyltransferase (GGT) increased in 17.2% of patients. GGT increased resulted in dose delay, dose reduction, and treatment withdrawal in 21.4%, 3.4% and 12.4% of patients, respectively. Grade 3 ALT increased occurred in 2.8%, Grade 3 blood alkaline phosphatase increased occurred in 0.7%, and Grade 3 AST increased in 0.7% of patients. Increased blood bilirubin was noted in 2.8% of patients, with Grade 3 occurring in 1.4% of patients.

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 anaemia in 10.3% of patients. Febrile neutropenia Grade 3 occurred in 3.4% of patients. Thrombocytopenia and neutropenia led to discontinuation of treatment in 1.4% and 0.7% of patients, respectively.

Pain

Pain of severity Grade 3 occurred in 2.8% of patients treated with ZYNLONTA. Grade 3 pain, neck pain, non-cardiac chest pain and facial pain was noted in 0.7% of patients each.

Skin reactions and nail disorders

Severe skin reactions and nail disorders occurred in patients treated with ZYNLONTA. Grade 3 skin reactions and nail disorders occurred in 4.1% of patients and included photosensitivity reaction (2.1%), rash (0.7%), rash pustular (0.7%), rash maculo-papular (0.7%), and erythema (0.7%). One (1) patient (0.7%) each discontinued ZYNLONTA due to Grade 2 photosensitivity reaction and Grade 1 pruritus.

Post-marketing experience

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

Hepatobiliary disorders: severe liver injury (frequency unknown).

Skin and subcutaneous tissue disorders: telangiectasia, blister, rash vesicular, cutaneous collagenous vasculopathy (frequency unknown).

Vascular disorders: capillary leak syndrome (frequency unknown).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In case of overdose, patients should be closely monitored for signs or symptoms of toxicity and appropriate symptomatic treatment instituted.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Loncastuximab tesirine is an antibody-drug conjugate (ADC) targeting CD19. 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 PBD dimer and alkylating agent.

Upon binding to CD19, loncastuximab tesirine is internalised 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.

Clinical trials

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), as defined by the 2016 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, after at least 2 prior systemic regimens. The study excluded patients with bulky disease (defined as any tumour ≥10 cm in the longest dimension), due to lower response rate, and active central nervous system lymphoma. Patients received ZYNLONTA 0.15 mg/kg every 21 days for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles. Patients received treatment for 1 year, or beyond if they were clinically benefitting, or until progressive disease or unacceptable toxicity.

Among the 145 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 26).

Of the 145 patients enrolled, the median age was 66 years (range 23 to 94) while 14% were 75 years of age and older, 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian. The diagnosis as per the 2016 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues was DLBCL not otherwise specified (NOS) in 88% (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 therapies was 3 (range 2 to 7). 43% of the patients received 2 prior therapies whereas 23% received 3 prior therapies and 33% received more than 3 prior therapies. 63% of patients had refractory disease, 17% with prior stem cell transplant, and 10% with prior chimeric antigen receptor (CAR) T-cell therapy.

Efficacy was evaluated on the basis of overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria (Table 3). The median follow-up was 7.75 months (range: 0.3 to 42.6 months).

Table 3: Efficacy results in patients with relapsed or refractory DLBCL

Efficacy parameter	**ZYNLONTA N = 145**
Overall response rate by IRC[a], (95% CI)	48.3% (39.9, 56.7)
Complete response rate (95% CI)	24.8% (18.0, 32.7)
Median duration of response (95% CI), months	13.4 (6.9, NE) (N=70)

CI = confidence interval, NE = not estimable
[a] IRC = independent review committee using Lugano 2014 criteria

Immunogenicity

As with all therapeutic proteins, there is potential for an immune response in patients treated with loncastuximab tesirine. In ADCT-402-201 (LOTIS-2), 0 of 134 patients tested positive for antibodies against loncastuximab tesirine after treatment, including the long-term follow up.

Elderly population

Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in the ADCT-402-201 (LOTIS-2) study, 55% were 65 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

5.2 PHARMACOKINETIC PROPERTIES

The exposure of loncastuximab tesirine at the recommended dosage in Cycle 1 and Cycle 2 based on study ADCT-204-201 (LOTIS-2) is shown in Table 4. The time to reach steady state was approximately 15 weeks.

Table 4: Loncastuximab tesirine exposure parameters

Cycle	C_{max} (ng/mL)	AUC_{tau}* (ng*day/mL)	**T_{half} (day)**	**CL (L/day)**	**AI (CV)**
1	2,436 (38.8)	19,775 (53.7)	**8.85 (53.5)**	**0.459 (48.3)**	-
2	2,736 (35.6)	26,902 (33.4)	**15.3 (31.7)**	**0.331 (32.0)**	**1.65 (18.5)**

C_{max} = Maximum predicted serum concentration; AUC_{tau} = Area under curve over the dosing interval.
CL = apparent clearance for Cycle 1 and Cycle 2; AI = accumulation index; CV = coefficient of variation.
Data presented as geometric mean and coefficient of variation (%CV).

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 from study ADCT-402-201 (LOTIS-2) following 150 µg/kg Q3W at Cycle 1 and Cycle 2 was 4.26 L (40.3%) in Cycle 1 and 6.42 L (36.7%) in Cycle 2.

Metabolism

The monoclonal antibody portion of loncastuximab tesirine is expected to be metabolised into small peptides by catabolic pathways. The small molecule cytotoxin, SG3199, is metabolised by CYP3A4/5 and a non-CYP-mediated mechanism *in vitro*.

Excretion

The geometric mean (CV%) loncastuximab tesirine clearance decreased 0.459 L/day (48.3%) from Cycle 1 to 0.331 L/day (32.0%) in Cycle 2. The mean (standard deviation) half-life of loncastuximab tesirine was 8.85 (53.5%) days in Cycle 1 and 15.3 (31.7%) days in Cycle 2.

The major excretion pathways of SG3199 have not been studied in humans, therefore, no clinical data is available. Data collected in an animal model (rat) show main elimination via faeces, with only minimal renal excretion.

Special Populations

No clinically significant differences in the pharmacokinetics of loncastuximab tesirine were observed based on age (20 - 94 years), sex, race (White vs. Black), body weight (42.1 to 160.5 kg), ECOG status (0 to 2).

Patients with renal impairment

The clearance of loncastuximab tesirine in patients with mild to moderate renal impairment (CrCl 30 to <90 mL/min using the Cockcroft-Gault equation) was not significantly different from patients with normal renal function. ZYNLONTA has not been studied in patients with severe renal impairment (CrCl 15 to 29 mL/min). The effect of severe renal impairment, and end-stage renal disease, with or without haemodialysis, on loncastuximab tesirine pharmacokinetics is unknown.

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

Patients with hepatic impairment

Mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 × ULN and any AST) may increase the exposure of unconjugated SG3199, however there was no clinically significant effect on loncastuximab tesirine pharmacokinetics.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

SG3199 was genotoxic via a clastogenic mechanism in an *in vitro* micronucleus test and a chromosome aberration assay using human lymphocytes. 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. SG3199 could be expected to be mutagenic.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine, histidine hydrochloride monohydrate, sucrose, and polysorbate 20.

6.2 INCOMPATIBILITIES

This medicine must not be mixed with or administered as an infusion with other medicinal products except those mentioned in section 4.2 Dose and method of administration.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Keep the vial in the outer carton in order to protect from light.

Reconstituted solution

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, the reconstituted solution should not be stored longer than 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 the diluted solution should not be stored longer than 24 hours refrigerated (2°C - 8°C) or 8 hours at room temperature (20°C - 25°C).

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

6.5 NATURE AND CONTENTS OF CONTAINER

ZYNLONTA is supplied in a pack containing one single vial (clear Type 1 glass) closed with a stopper (fluoropolymer-coated rubber), with an aluminium seal with plastic flip-off cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

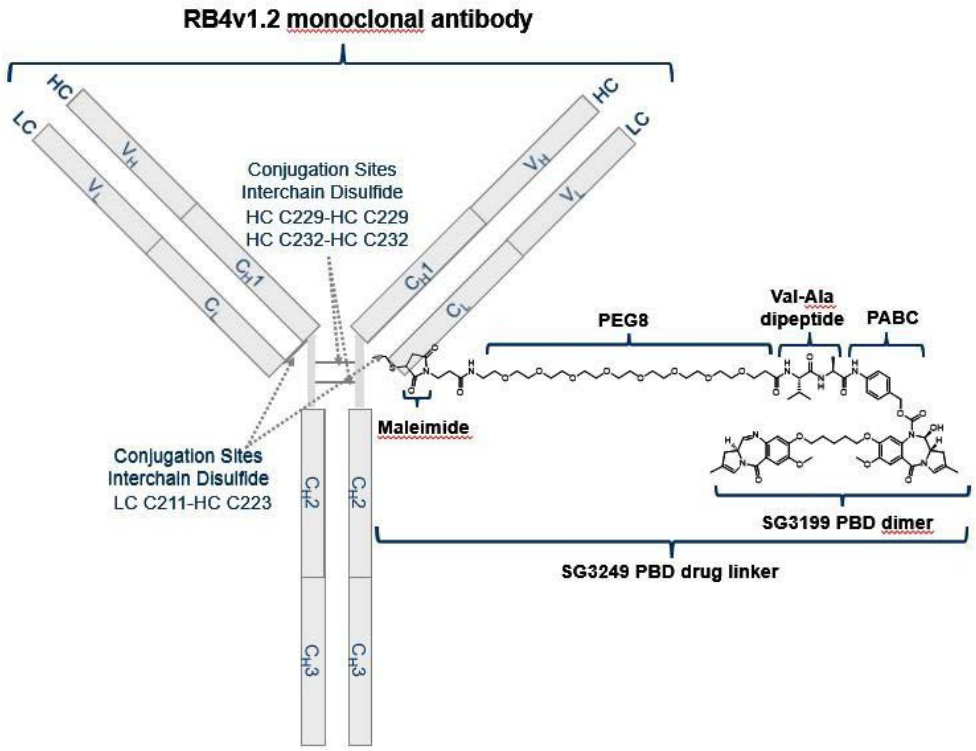

Figure 1: Loncastuximab tesirine drug substance schematic

Loncastuximab tesirine is a CD19-targeted antibody-drug conjugate (ADC), consisting of a humanised immunoglobulin G1 (IgG1) kappa monoclonal antibody (RB4v1.2) directed against CD19 and conjugated through a protease-cleavable valine-alanine linker to SG3199, a PBD dimer cytotoxic drug. The toxin SG3199 attached to the linker is designated as SG3249, also known as tesirine.

CAS number:

1879918-31-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Swedish Orphan Biovitrum Pty Ltd
Suite 3, Level 2, Building D,
12-24 Talavera Road,
Macquarie Park, NSW 2113

https://au.sobi.com

Medical enquiries: 1800 570 605.

9 DATE OF FIRST APPROVAL

DD MMM YYYY

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New document