SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Zynlonta 10 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for concentrate for solution for infusion contains 10 mg of loncastuximab tesirine.

After reconstitution, each mL contains 5 mg of loncastuximab tesirine.

Loncastuximab tesirine is a CD19-directed antibody and alkylating agent conjugate, consisting of a humanised IgG1 kappa monoclonal antibody, produced in Chinese Hamster Ovary cells by recombinant DNA technology, and 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.

Excipient with known effect
Each vial of Zynlonta contains 0.4 mg (0.2 mg/mL) of polysorbate 20.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology 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.

Posology

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.

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 21-day interval between doses.

Dose modification

For dose modification for haematologic and non-haematologic adverse reactions (see section 4.8), 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 (see section 4.8)	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 (see section 4.8)	Platelet count less than 50,000/mcL	Withhold Zynlonta until platelet count returns to 50,000/mcL or higher
Non-haematologic adverse reactions		
Oedema or effusion (see section 4.8)	Grade 2 or higher	Withhold Zynlonta until the toxicity resolves to Grade 1 or less
Other adverse reactions (see section 4.8)	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 requires dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the dose of 0.075 mg/kg for Cycle 3.

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

Elderly

No dose adjustment of Zynlonta is required in patients ≥65 years of age (see section 5.1).

Renal impairment

No dose adjustment of Zynlonta is required for patients with mild to moderate renal impairment (see section 5.2).

Zynlonta has not been studied in patients with severe renal impairment (CLcr 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. Additional monitoring for adverse reactions may be warranted in these patients when loncastuximab tesirine is administered.

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

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).

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 adverse reactions is recommended.

Paediatric population

The safety and efficacy of loncastuximab tesirine in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of 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). The infusion site should be monitored for possible subcutaneous infiltration during medicinal product administration.

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.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains a cytotoxic component, which is covalently attached to the monoclonal antibody (see special handling and disposal procedures in section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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).

Patients should be monitored for new or worsening oedema or effusions. Zynlonta should be withheld for Grade 2 or greater oedema 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 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 (see section 4.2). 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).

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).

Infections

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

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 section 4.2).

Photosensitivity and cutaneous reactions

Serious cutaneous reactions have been reported in patients treated with Zynlonta. In clinical studies with Zynlonta oral and topical corticosteroids and anti-pruritic therapy were used to treat cutaneous reactions (see section 4.8).

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). 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 (see section 5.3).

Embryo-foetal toxicity

Zynlonta may cause embryo-foetal 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 foetus. 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

In non-clinical studies, loncastuximab tesirine was associated with testicular toxicity so may impair male reproductive function and fertility (see section 5.3).

Polysorbates

This medicinal product contains 0.4 mg of polysorbate 20 in each vial, which is equivalent to 0.2 mg/mL.

Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

No clinically important PK interactions are expected (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/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.

Pregnancy

There are no data on the use of loncastuximab tesirine in pregnant women. No animal reproduction studies were conducted with loncastuximab tesirine. Zynlonta may cause embryo-foetal toxicity when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Zynlonta is not recommended during pregnancy unless the potential benefit for the woman outweighs the potential risk to the foetus. Zynlonta is not recommended in women of childbearing potential not using contraception.

Pregnancy testing is advised prior to initiating Zynlonta.

Breast-feeding

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. Breast-feeding should be discontinued during treatment with Zynlonta and for at least 3 months after the last dose.

Fertility

Based on the results from animal studies, loncastuximab tesirine may impair male fertility (see section 5.3). Therefore, men being treated with this medicine should be advised to consider having sperm samples preserved and stored before initiating treatment.

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 Undesirable effects

Summary of the safety profile

The most frequent reported adverse reactions with loncastuximab tesirine were γ-glutamyltransferase increased (35.8%), neutropenia (34.9%), fatigue (30.2%), anaemia (28.8%), thrombocytopenia (28.4%), nausea (26.5%), peripheral oedema (23.3%), and rash (20.0%).The most frequent severe adverse reactions (≥ Grade 3) were neutropenia (24.2%), γ-glutamyltransferase increased (17.2%), thrombocytopenia (15.8%), anaemia (11.6%) and infections (9.8%).

The most frequent serious adverse reactions were febrile neutropenia (3.3%), abdominal pain, dyspnoea and pleural effusion (1.9% each). Lung infection was identified as an adverse reaction associated with fatal outcome (0.5%).

The most frequent adverse reactions leading to treatment withdrawal were γ-glutamyltransferase increased (8.8%), peripheral oedema (2.8%), thrombocytopenia (1.9%), pleural and pericardial effusion (1.4% each).

The frequency of dose modification or interruption due to adverse reactions was 47.4%. The most frequent adverse reaction leading to dose reduction was γ-glutamyltransferase increased (3.3%), and the most frequent adverse reactions leading to dose delay were γ-glutamyltransferase increased (17.7%), neutropenia (11.2%) and thrombocytopenia (7.9%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on 215 patients with relapsed or refractory DLBCL, who received Zynlonta alone as an intravenous infusion at the recommended initial dose (0.15 mg/kg) in two monotherapy studies, of whom 145 patients participated in the Phase 2 pivotal study ADCT-402-201 (LOTIS-2) and 70 patients participated in the Phase 1 study (ADCT-402-101). These patients were exposed to Zynlonta during a median of 45 days (range 1 to 569 days).

Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies in the clinical studies, 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.

Adverse reactions are presented according to the MedDRA system organ class (SOC) and classified, by frequency, as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented by seriousness from highest to lowest.

Table 2: Adverse reactions reported for Zynlonta in adult patients with relapsed or refractory DLBCL

MedDRA SOC	Very common	Common	Uncommon	Not known[d]
Infections and infestations		Pneumonia[a] (includes lung infection) Upper respiratory tract infection Sepsis Lower respiratory tract infection		
Blood and lymphatic system disorders	Anaemia Neutropenia Thrombocytopenia	Febrile neutropenia		
Metabolism and nutrition disorders	Decreased appetite	Fluid retention	Fluid overload	
Nervous system disorders		Lethargy		
Cardiac disorders		Pericardial effusion	Pericarditis	
Respiratory, thoracic and mediastinal disorders	Pleural effusion Dyspnoea[b]			
Gastrointestinal disorders	Abdominal pain[c] Diarrhoea Nausea Vomiting Constipation	Ascites		
Skin and subcutaneous tissue disorders	Rash Pruritus Erythema	Bullous dermatitis Photosensitivity reaction Swelling face Maculopapular rash Pruritic rash Skin hyperpigmentation	Pustular rash	Telangiectasia Blister Rash vesicular Cutaneous collagenous vasculopathy

MedDRA SOC	Very common	Common	Uncommon	Not known[d]
Musculoskeletal and connective tissue disorders		Neck pain Pain in extremity Back pain Musculoskeletal pain Myalgia Musculoskeletal chest pain	Musculoskeletal discomfort Limb discomfort	
General disorders and administration site conditions	Oedema peripheral Fatigue	Face oedema Asthenia Peripheral swelling Swelling Non-cardiac chest pain	Generalised oedema Oedema	
Investigations	γ-glutamyltransferase increased Aspartate aminotransferase increased Alanine aminotransferase increased Blood alkaline phosphatase increased			

a Grade 5 associated adverse reactions
b Dyspnoea includes dyspnoea, and dyspnoea exertional
c Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper
d These 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.

Description of selected adverse reactions

Effusion and oedema
Serious effusion and oedema occurred in patients treated with Zynlonta. Grade ≥3 oedema and effusion occurred in 5.6% of patients. Grade 3 or 4 pericardial effusion occurred in 1.4% of patients. Grade 3 pleural effusion occurred in 2.8%, Grade 3 peripheral oedema and ascites in 1.4% each, and Grade 3 peripheral swelling in 0.5% of patients (see section 4.4). Effusion and oedema led to discontinuation of treatment in 5.1% of patients. There were no fatal events of effusion or oedema. Median time to onset for Grade ≥3 effusion and oedema was 115 days and 101 days, respectively (see section 4.4).

Myelosuppression

Treatment with Zynlonta can cause severe myelosuppression. Grade 3 or 4 neutropenia occurred in 24.2%, Grade 3 or 4 thrombocytopenia in 15.8%, and Grade 3 or 4 anaemia in 11.6% of patients. Febrile neutropenia occurred in 3.3% of patients (see section 4.4). Thrombocytopenia and neutropenia led to discontinuation of treatment in 1.9% and 0.5% of patients, respectively. No patients discontinued treatment due to anaemia (see section 4.4). Median time to onset for Grade 3 or 4 neutropenia, thrombocytopenia and anaemia was 36.0 days, 28.5 days, and 22.0 days, respectively (see section 4.4).

Infections
Fatal and serious infections, including opportunistic infections and sepsis, occurred in patients treated with Zynlonta. Grade ≥3 infections occurred in 9.8% of patients with an associated fatal infection in 0.5% of patients (see section 4.4). Infections led to discontinuation of treatment in 0.9% of patients.

Cutaneous reactions
Severe cutaneous reactions occurred in patients treated with Zynlonta. Grade 3 cutaneous reactions occurred in 3.7% and included photosensitivity reaction (1.4%), rash (0.9%), rash pustular (0.5%), rash maculo-papular (0.5%), and erythema (0.5%) (see section 4.4). There were no Grade 4 or Grade 5 cutaneous reactions. Three (3) patients (1.4%) discontinued Zynlonta due to Grade 1-2 cutaneous reactions, and no patients discontinued Zynlonta due to a severe cutaneous reaction. Median time to onset for Grade 3 photosensitivity reactions was 32.0 days and for Grade 3 non-photosensitivity cutaneous reactions was 56.0 days (see section 4.4).

Serious cutaneous reactions have been reported in patients treated with Zynlonta. In clinical studies with Zynlonta oral and topical corticosteroids and anti-pruritic therapy were used to treat cutaneous reactions (see section 4.4).

Liver function tests
Abnormal liver function tests of severity Grade ≥3 occurred in 19.5% of patients, with Grade 3 or 4 γ-glutamyltransferase (GGT) increased in 17.2% of patients. GGT increase resulted in dose delay, dose reduction, and treatment withdrawal in 17.7%, 3.3%, and 8.8% of patients, respectively. Grade 3 alanine aminotransferase increased occurred in 2.8%, blood alkaline phosphatase increased in 1.4%, and aspartate aminotransferase increased in 0.9% of patients. Increased blood bilirubin was noted in 2.8% of patients, with Grade 3 occurring in 1.4% of patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX22

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.

Pharmacodynamic effects

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, liver function test abnormalities and increased γ-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.

Clinical efficacy and safety

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 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 3 weeks 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), with 60% receiving three or more cycles and 34% receiving five or more cycles. Twelve (12) patients received stem cell transplantation directly following treatment with Zynlonta.

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 was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 7%. The median number of prior therapies was 3 (range 2 to 7). 43% of the patients received 2 prior therapies whereas 24% received 3 prior therapies and 32% received more than 3 prior therapies. 63% of patients had refractory disease, 17% with prior stem cell transplant, and 9% 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 time was 7.8 months (range 0.3 to 31).

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 time to response (range), months	1.3 (1.1, 8.1)
Duration of overall response	**N = 70**
Median (95% CI), months	13.4 (6.9, NE)
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.

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.

Paediatric population
The MHRA has deferred the obligation to submit the results of studies with Zynlonta in one or more subsets of the paediatric population in treatment of B-cell non-Hodgkin Lymphoma (B-NHL) (see section 4.2 for information on paediatric use).

Conditional approval
This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The MHRA will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The exposure of loncastuximab tesirine at the approved recommended dosage in Cycle 2 and at steady state is shown in Table 4. Loncastuximab tesirine

steady state C_{max} was 39.0% lower than the C_{max} after the second dose. The time to reach steady state was approximately 15 weeks.

Table 4: Loncastuximab tesirine exposure parameters

Time	**C_{max} (ng/mL)**	**AUC_{tau} (ng • day/mL)**
Cycle 2	2795 (36.4%)	22,082 (46.0%)
Steady state	1705 (31.6%)	16,265 (34.9%)

C_{max} = Maximum predicted serum concentration; AUC_{tau} = Area under curve over the dosing interval.
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 was 7.14 (22.9%) L.

In Vitro Studies
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.

Metabolism/biotransformation
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 *in vitro*.

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.

Elimination
The geometric mean (CV%) loncastuximab tesirine clearance decreased with time from 0.34 L/day (53.2%) after a single dose to 0.26 L/day (37.2%) at steady state. The mean (standard deviation) half-life of loncastuximab tesirine was 15.8 (6.26) days in Cycle 1 and 20.5 (5.72) days at steady state.

Excretion
The major excretion pathways of SG3199 have not been studied in humans. Data collected in an animal model (rat) show minimal renal excretion. No clinical data are available.

Specific 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) or mild to moderate renal impairment (CLcr 30 to <90 mL/min using the Cockcroft-Gault equation).

Patients with renal impairment
The clearance 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.

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

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 toxicity

No dedicated reproductive toxicity studies in animals have been conducted with loncastuximab tesirine.

However, the cytotoxic component of Zynlonta, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryo-foetal toxicity.

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 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.

Toxicities

In repeat-dose toxicity studies in cynomolgus monkeys, intravenous administration of loncastuximab tesirine was associated with renal toxicity including increased 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine monohydrochloride
Polysorbate 20 (E 432)
Sucrose

6.2 Incompatibilities

This medicinal product must not be mixed with or administered as an infusion with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

5 years

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□ - 8□) or 4 hours at room temperature (20□ - 25□), unless reconstitution has taken place in controlled and validated aseptic conditions. Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 4 hours refrigerated (2□ - 8□) or 4 hours at room temperature (20□ - 25□).

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□ - 8□) or 8 hours at room temperature (20□ - 25□), unless dilution has taken place in controlled and validated aseptic conditions. Chemical and physical in-use stability of the prepared solution for infusion has been demonstrated for up to 24 hours at room temperature (20□ - 25□).

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

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (clear Type 1 glass) closed with a stopper (fluoropolymer coated rubber), with an aluminium seal with plastic flip-off cap containing 10 mg loncastuximab tesirine. Pack size of one vial.

6.6 Special precautions for disposal

General precautions
Zynlonta contains a cytotoxic component and should be administered under the supervision of a physician experienced in the use of cytotoxic agents. Procedures for proper handling and disposal of antineoplastic and cytotoxic medicinal products should be used.

Proper aseptic technique throughout the handling of this medicinal product should be followed.

The reconstituted product contains no preservative and is intended for single-dose only.

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

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

Dose calculation

Calculate the total dose (mg) required based on the patient's weight and prescribed dose (see section 4.2).

- 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.
- 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.

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.

Disposal

Zynlonta is for single-use only.

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

7 MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum AB (publ)

SE-112 76 Stockholm

Sweden

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 30941/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/10/2025

10 DATE OF REVISION OF THE TEXT

16/02/2026