

**ANNEX I**  
**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 pyrrolbenzodiazepine (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.

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 pyrrolbenzodiazepine (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 nonhaematologic adverse reactions (see section 4.8), see Table 1 below.

**Table 1: Zynlonta dose modification for haematologic and nonhaematologic adverse reactions**

<b>Adverse reactions</b>	<b>Severity</b>	<b>Dose modification</b>
<b>Haematologic adverse reactions</b>		
Neutropenia (see section 4.8)	Absolute neutrophil count less than $1 \times 10^9/L$	Withhold Zynlonta until neutrophil count returns to $1 \times 10^9/L$ 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
<b>Nonhaematologic adverse reactions</b>		
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  $\geq 65$  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 ( $CL_{cr}$  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  $\leq$  upper limit of normal [ULN] and aspartate aminotransferase [AST]  $>$  ULN or total bilirubin  $>1$  to  $1.5 \times$  ULN and any AST).

Zynlonta has not been studied in patients with moderate or severe hepatic impairment (total bilirubin  $>1.5 \times$  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).

#### 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. Cytopenias 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, 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).

### **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  $\gamma$ -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 ( $\geq$  Grade 3) were neutropenia (24.2%),  $\gamma$ -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  $\gamma$ -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  $\gamma$ -glutamyltransferase increased (3.3%), and the most frequent adverse reactions leading to dose delay were  $\gamma$ -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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ), rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ) and very rare ( $< 1/10\ 000$ ), 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
Infections and infestations		Pneumonia <sup>a</sup> (includes lung infection) Upper respiratory tract infection 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 <sup>b</sup>		
Gastrointestinal disorders	Abdominal pain <sup>c</sup> Diarrhoea Nausea Vomiting Constipation	Ascites	
Skin and subcutaneous tissue disorders	Rash Pruritus Erythema	Photosensitivity reaction Maculopapular rash Skin hyperpigmentation Pruritic rash Swelling face Bullous dermatitis	Pustular rash

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	$\gamma$ -glutamyltransferase increased Aspartate aminotransferase increased Alanine aminotransferase increased Blood alkaline phosphatase increased		
<p>a Grade 5 associated adverse reactions</p> <p>b Dyspnoea includes dyspnoea, and dyspnoea exertional</p> <p>c Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper</p>			

### Description of selected adverse reactions

#### *Effusion and oedema*

Serious effusion and oedema occurred in patients treated with Zynlonta. Grade  $\geq 3$  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  $\geq 3$  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, occurred in patients treated with Zynlonta. Grade  $\geq 3$  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  $\geq 3$  occurred in 19.5% of patients, with Grade 3 or 4  $\gamma$ -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.

#### *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.

**Skin and Subcutaneous Tissue Disorders:** telangiectasia, blister, rash vesicular (frequency unknown).

#### 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 national reporting system listed in [Appendix V](#).

## **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  $\geq 2$  adverse reactions, including skin and nail reactions, liver function test abnormalities and increased  $\gamma$ -glutamyltransferase.

### Cardiac electrophysiology

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

### 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  $\geq 10$  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**

<b>Efficacy parameter</b>	<b>Zynlonta N = 145</b>
<b>Overall response rate by IRC<sup>a</sup>, (95% CI)</b>	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)
<b>Duration of overall response</b>	<b>N = 70</b>
Median (95% CI), months	13.4 (6.9, NE)
CI = confidence interval, NE = not estimable	
<sup>a</sup> 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 European Medicines Agency 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 European Medicines Agency 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**

<b>Time</b>	<b><math>C_{max}</math> (ng/mL)</b>	<b><math>AUC_{tau}</math> (ng • day/mL)</b>
<b>Cycle 2</b>	2795 (36.4%)	22,082 (46.0%)
<b>Steady state</b>	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 (CL<sub>cr</sub> 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 (CL<sub>cr</sub> 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  $\leq$  ULN and AST  $>$  ULN, or total bilirubin  $>1$  to  $1.5 \times$  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  $>1.5 \times$  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  
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

4 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°C - 8°C) or 4 hours at room temperature (20°C - 25°C), 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°C - 8°C) or 4 hours at room temperature (20°C - 25°C).

### Diluted solution

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

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 (teflon 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 and other handling**

### 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)**

EU/1/22/1695/001

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 December 2022

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.



## **ANNEX II**

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

## **A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

### Name and address of the manufacturer of the biological active substance

BSP Pharmaceuticals S.p.A  
Via Appia Km 65,561  
04013 Latina Scalo (LT)  
Italy

### Name and address of the manufacturer responsible for batch release

Swedish Orphan Biovitrum AB (publ)  
Strandbergsgatan 49  
SE-112 51 Stockholm  
Sweden

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Zynlonta in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the phototoxicity risk minimisation material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

An additional risk minimisation material is aimed at reducing the risk of photosensitivity reactions.

The MAH shall ensure that in each Member State where Zynlonta is marketed, all healthcare professionals who are expected to prescribe Zynlonta and all patients who are expected to use Zynlonta are provided with the following risk minimisation material:

- Patient Alert Card
  - Patient Alert Cards are provided to Zynlonta prescribing physicians for distribution to patients receiving Zynlonta (loncastuximab tesirine) for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL)
  - This card should be carried by patients at all times and provides the following key important safety information to patients:
    - Zynlonta treatment may increase the risk of photosensitivity reactions in patients
    - Signs and symptoms of photosensitivity reactions
    - Instructions to avoid exposure to direct and indirect sunlight and to contact a healthcare professional when any skin eruption occurs
    - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Zynlonta

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

<b>Description</b>	<b>Due date</b>
In order to confirm the efficacy and safety of loncastuximab tesirine in 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, the MAH should submit the final results of study ADCT-402-311 (LOTIS 5), a Phase 3 study comparing loncastuximab tesirine combined with rituximab (Lonca R) versus immunochemotherapy in patients with relapsed or refractory DLBCL.	Q4/2025
In order to confirm the safety of loncastuximab tesirine in 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, the MAH should submit the final results from study ADCT-402-201 a Phase 2, single-arm study investigating the efficacy and safety of loncastuximab tesirine in patients with relapsed or refractory DLBCL.	Q4/2023

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Zynlonta 10 mg powder for concentrate for solution for infusion  
loncastuximab tesirine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 10 mg of loncastuximab tesirine.  
After reconstitution, each mL contains 5 mg of loncastuximab tesirine.

**3. LIST OF EXCIPIENTS**

L-histidine, L-histidine monohydrochloride, polysorbate 20, sucrose

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for concentrate for solution for infusion  
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use after reconstitution and dilution.  
Single-use only.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Cytotoxic  
Do not shake.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.  
Keep the vial in the outer carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Swedish Orphan Biovitrum AB (publ)  
SE-112 76 Stockholm  
Sweden

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1695/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Zynlonta 10 mg powder for concentrate  
loncastuximab tesirine  
Intravenous use

**2. METHOD OF ADMINISTRATION**

IV after reconstitution and dilution

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

10 mg

**6. OTHER**

Cytotoxic



**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Zynlonta 10 mg powder for concentrate for solution for infusion loncastuximab tesirine

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Zynlonta is and what it is used for
2. What you need to know before you are given Zynlonta
3. How you are given Zynlonta
4. Possible side effects
5. How to store Zynlonta
6. Contents of the pack and other information

#### 1. What Zynlonta is and what it is used for

Zynlonta is a cancer medicine that contains the active substance loncastuximab tesirine.

Zynlonta is used to treat adults with a certain type of cancer called **diffuse large B-cell lymphoma (DLBCL)** that:

- has come back (relapsed) after two or more treatments, or that
- did not respond to previous treatment (refractory).

Diffuse large B-cell lymphoma is a cancer that develops from a type of white blood cell called B-lymphocyte (also called B-cell).

Talk to your doctor or nurse if you have any questions about how Zynlonta works or why this medicine has been prescribed for you.

#### How does Zynlonta work?

Loncastuximab tesirine consist of 2 parts; an antibody (a type of protein designed to recognize and attach to a specific target) and a cytotoxic agent (a medicine able to kill cells, including cancer cells). The antibody in this medicine is designed to attach to CD19, a protein that is found on the surface of B cells. When the antibody binds to these cells, including the cancer cells, the medicine enters the cells and kills them.

#### 2. What you need to know before you are given Zynlonta

**You must not be given Zynlonta** if you are **allergic to loncastuximab tesirine** or any of the other **ingredients** of this medicine (listed in section 6).

## Warnings and precautions

**Talk to your doctor or nurse before you are given Zynlonta** if you:

- have an **active infection** or have had one recently
- have **liver problems**; symptoms may include skin and eyes appearing yellowish (jaundice). Your doctor will monitor you for side effects during treatment.
- are **pregnant or plan to become pregnant**. Zynlonta can harm your unborn baby (see section “Pregnancy and breast-feeding and fertility” for further information).

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

### *Infections*

Serious infections, including infections that can cause death, have occurred in people treated with Zynlonta. **Tell your doctor or nurse straight away** if you have new or worsening signs or symptoms of infection, which are listed in section 4, under ‘Serious side effects’.

### *Fluid retention*

Your body may hold too much fluid during treatment with Zynlonta. This can be serious. **Tell your doctor or nurse straight away** if you have any signs or symptoms of fluid retention, which are listed in section 4, under ‘Serious side effects’. Your doctor will give appropriate treatment for the fluid retention. If you have serious swelling your doctor may stop treatment until the swelling goes down.

### *Low blood cell counts* (platelets, red blood cells, and white blood cells)

Low levels of certain blood cells (low blood cell counts) can be serious or severe. Your doctor or nurse will monitor your blood cell counts during treatment with Zynlonta. **Tell your doctor or nurse straight away** if you have any signs and symptoms of infection, which are listed in section 4, under ‘Serious side effects’. Low blood cell counts could be responsible for your infection.

### *Skin reactions*

Serious skin reactions have occurred in people treated with Zynlonta. Exposure to sunlight (including through glass or car windows) may cause severe sunburn. It is important to wear sunscreen and appropriate clothing to ensure you do not burn. **Tell your doctor or nurse straight away** if you get new or worsening severe skin reactions. Signs and symptoms are listed in section 4, under ‘Possible side effects’.

### **Children and adolescents**

This medicine should not be given to children or young people under the age of 18. This is because there is no information about its use in this age group.

### **Other medicines and Zynlonta**

Tell your doctor if you are taking, have recently taken or might **take any other medicines**.

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

**Women of child-bearing potential must use effective contraception** during treatment with Zynlonta, and for 10 months after the last dose.

**Men** with partners of child-bearing potential **must use effective contraception** during treatment with Zynlonta, and for 7 months after the last dose.

Talk to your doctor about effective contraception.

### **Pregnancy**

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

### **Breast-feeding**

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

### **Fertility**

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

### **Driving and using machines**

Zynlonta has no or negligible influence on your ability to drive and use machines. If you get infusion-related reactions or if you feel tired, weak or dizzy (see section 4) do not drive, cycle or use tools or machines until you feel better.

See section 4 for more information about side effects.

## **3. How you are given Zynlonta**

Zynlonta is given under supervision of a doctor experienced in giving such treatments. It is given **into a vein** as a drip (infusion) **over a period of 30 minutes**.

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

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

<b>Recommended dose</b>	<b>Cycle</b>
0.15 mg per kg every 21 days	1 <sup>st</sup> cycle
0.15 mg per kg every 21 days	2 <sup>nd</sup> cycle
0.075 mg per kg every 21 days	3 <sup>rd</sup> cycle onwards

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

### **Taking dexamethasone with Zynlonta**

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

You will be given 4 mg of dexamethasone either by mouth or into your vein twice a day for three days, beginning the day before you receive Zynlonta treatment.

If you do not receive dexamethasone the day before your treatment, then it must be given at least 2 hours before you are given Zynlonta.

### **How often will you be given Zynlonta**

Zynlonta is usually given every 3 weeks (on day 1 of a 21-day cycle).

- Your doctor will give you medicines before each infusion to lower your chance of side effects.
- Your doctor may stop your treatment, delay your treatment, or change your dose of Zynlonta if you have severe side effects (see section 4 possible side effects).
- Your doctor will do regular blood tests to check for side effects of Zynlonta.
- Your doctor will decide how many treatment cycles you need.

### **If you are given more Zynlonta than you should**

Since the infusion is given to you by your doctor or other appropriately trained staff, an overdose is unlikely. If you inadvertently receive too much medicine, your doctor will monitor you and give you additional treatment as required.

### **If you miss a dose of Zynlonta**

If you miss a dose of Zynlonta, it should be given as soon as possible. You might need to reschedule receiving the next planned dose to ensure that it is given 21 days after the missed dose. The 21-day interval between doses should be maintained.

### **If you stop receiving Zynlonta**

You should not stop the therapy early without talking with your doctor first.

The therapy for lymphoma with Zynlonta usually requires a number of infusions. The number of infusions that you receive will depend on how you are responding to treatment. Therefore, even if you see your symptoms improve, you should continue to take Zynlonta until your doctor decides that your medicine should be stopped. If the treatment is stopped too early, your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects have been reported with this medicine:

### **Serious side effects**

#### ***Infections***

Serious infections, including infections that can cause death, have occurred in people treated with Zynlonta. **Tell your doctor or nurse straight away** if you notice any of the following signs and symptoms:

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

#### ***Fluid retention***

Your body may hold too much fluid during treatment with Zynlonta. This can be serious. You can get swelling in various parts of your body including your hands, feet (very common) and abdomen (common), or around internal organs such as your heart (common) and lungs (very common).

**Tell your doctor or nurse straight away** if you notice any of the following signs and symptoms:

- have chest pain (common)
- difficulty breathing (very common)
- swelling in any part of your body (very common)

#### ***Low blood cell counts***

Low blood cell counts (very common) can be serious or severe. Your doctor or nurse will monitor your blood counts during treatment with Zynlonta. **Tell your doctor or nurse straight away** if you notice any bruising or bleeding, or any of the signs and symptoms of infections above.

#### ***Skin reactions***

Skin reactions (common) have occurred in people treated with Zynlonta. Some of these can be serious.

**Tell your doctor or nurse straight away** if you get new or worsening severe skin reactions, including:

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

## Other side effects

Tell your doctor or nurse if you notice any of the following side effects:

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

- tiredness and pale skin
- abnormal blood tests showing:
  - o low levels of neutrophils, a type of white blood cell that fight infection, sometimes with fever
  - o low blood platelet count which can lead to bleeding and bruising
  - o liver problems
- loss of appetite
- feeling sick or vomiting
- diarrhoea
- stomach pain
- constipation
- reddening of the skin
- rash
- itching.

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

- infection of the lungs including bronchitis or pneumonia
- nose and throat infection
- rash characterised by a flat, red area on the skin that is covered with small, raised bumps
- muscle pain
- joint pain
- back and neck pain
- pain in the arms and legs
- lack of energy.

**Uncommon:** may affect less than 1 in 10 people

- pus filled raised bumps on the skin
- limb discomfort
- muscle and bone discomfort
- inflammation of the membrane around the heart.

**Not known:** frequency cannot be estimated from the available data

- spider veins (broken blood vessels located near surface of skin)
- blisters
- rash consisting of tiny-to-small fluid-filled blisters

## Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Zynlonta

Zynlonta will be stored by the doctor and pharmacist at the hospital or clinic where you are treated. Your doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

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

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

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

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

Your doctor or pharmacist is responsible for disposing of any unused Zynlonta correctly. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Zynlonta contains**

- The **active substance** is loncastuximab tesirine. Each vial contains 10 mg of loncastuximab tesirine. After reconstitution, each mL contains 5 mg of loncastuximab tesirine.
- The **other ingredients** are: L-histidine, L-histidine monohydrochloride, polysorbate 20, sucrose.

### **What Zynlonta looks like and contents of the pack**

This medicine is a white to off-white powder, which has a cake-like appearance. It comes in a glass vial and is for single use only. The powder needs to be reconstituted and diluted before infusion.

Each pack contains 1 vial.

### **Marketing Authorisation Holder**

Swedish Orphan Biovitrum AB (publ)  
SE-112 76 Stockholm  
Sweden

### **Manufacturer**

Swedish Orphan Biovitrum AB (publ)  
Strandbergsgatan 49  
SE-112 51 Stockholm  
Sweden

### **This leaflet was last revised in**

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

### **Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

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The following information is intended for healthcare professionals only:

Procedures for proper handling and disposal of anticancer medicinal products should be considered.

#### 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.

#### Reconstituted solution

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

#### Diluted solution

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