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

AUSTRALIAN PRODUCT INFORMATION - VYLOY™ (ZOLBETUXIMAB)

1 NAME OF THE MEDICINE

Zolbetuximab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains an extractable amount of 100 mg zolbetuximab after reconstitution for a final concentration of 20 mg/mL.

Zolbetuximab is produced in Chinese hamster ovary cells by recombinant DNA technology.

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

3 PHARMACEUTICAL FORM

Single-dose vials containing sterile, preservative-free, white to off-white lyophilised powder for reconstitution for intravenous infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VYLOY, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (GOJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive (see section 4.2 Dose and method of administration).

4.2 DOSE AND METHOD OF ADMINISTRATION

General

Treatment with VYLOY should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.

Patient Selection

Select patients with locally advanced unresectable or metastatic HER2-negative gastric or GOJ adenocarcinoma whose tumours are CLDN18.2 positive (defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining) as determined by a validated test, for treatment with VYLOY in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1 Pharmacodynamic Properties).

Prior to Administration

If a patient is experiencing nausea and/or vomiting prior to administration of VYLOY, the symptoms should be resolved to Grade ≤1 before administering the first infusion.

Recommended Pretreatment

Prior to each infusion of VYLOY, premedicate patients with a combination of antiemetics (e.g., NK-1 receptor blockers and/or 5-HT3 receptor blockers, as well as other drugs as indicated), for the prevention of nausea and vomiting (see section 4.4 Special Warnings and Precautions for Use).

Dosage

Table 1. Recommended VYLOY Dosage Based on Body Surface Area

Single Loading Dose	Maintenance Doses	Duration of Therapy
800 mg/m^2 intravenously, Cycle 1, Day 1[a] Administer VYLOY in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1 Pharmacodynamic Properties).[b]	Beginning 3 weeks after the single loading dose, 600 mg/m^2 intravenously every 3 weeks or Beginning 2 weeks after the single loading dose, 400 mg/m^2 intravenously every 2 weeks[c] Administer VYLOY in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1 Pharmacodynamic Properties).[b]	Until disease progression or unacceptable toxicity.

a. The cycle duration of VYLOY is determined based on the respective chemotherapy backbone (see section 5.1 Pharmacodynamic Properties).
b. Refer to the fluoropyrimidine- or platinum-containing chemotherapy prescribing information regarding the dosing information for chemotherapy.
c. Based on pharmacokinetic modelling exercise (see section 5.1 Pharmacodynamic Properties).

Dose Modifications

No dose reduction for VYLOY is recommended. Adverse reactions for VYLOY are managed by infusion rate reduction, interruption, and/or discontinuation as presented in Table 2.

Table 2. Dose Modifications for VYLOY

Adverse Reaction	Severity[a]	Dose Modification
Hypersensitivity reactions (see section 4.4 Special Warnings and Precautions for Use)	Anaphylactic reaction, Suspected anaphylaxis, Grade 3 or 4	Immediately stop the infusion and permanently discontinue.
	Grade 2	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate[b] for the remaining infusion. • For the next infusion, premedicate and administer per the infusion rates in Table 3.
Infusion related reaction (see section 4.4 Special Warnings and Precautions for Use)	Grade 3 or 4	Immediately stop the infusion and permanently discontinue.
	Grade 2	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate[b] for the remaining infusion. • For the next infusion, premedicate and administer per the infusion rates in Table 3.
Nausea (see section 4.4 Special Warnings and Precautions for Use)	Grade 2 or 3	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate[b] for the remaining infusion • For the next infusion, administer per the infusion rates in Table 3.
Vomiting (see section 4.4 Special Warnings and Precautions for Use)	Grade 4	Permanently discontinue.
	Grade 2 or 3	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate[b] for the remaining infusion. • For the next infusion, administer per the infusion rates in Table 3.

a. Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

b. Reduced infusion rate should be determined per physician's clinical judgment based on patient tolerability, severity of toxicity, and previously tolerated infusion rate.

Special populations

Elderly

No dose adjustment is required in patients ≥65 years of age (see section 5.2 Pharmacokinetic Properties). Data for patients aged 75 years and older who received zolbetuximab are limited.

Paediatric population

The safety and efficacy of VYLOY in the paediatric population have not been established.

Renal impairment

No dose adjustment is required in patients with mild (creatinine clearance [CrCL] ≥60 to <90 mL/min) or moderate (CrCL ≥30 to <60 mL/min) renal impairment (see section 5.2 Pharmacokinetic Properties). VYLOY has only been evaluated in a limited number of patients with severe (CrCL ≥15 to <30 mL/min) renal impairment.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin [TB] ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN, or TB > 1 to 1.5 x ULN and any AST) (see section 5.2 Pharmacokinetic Properties). VYLOY has only been evaluated in a limited number of patients with moderate hepatic impairment (TB > 1.5 to 3 x ULN and any AST) and has not been evaluated in patients with severe hepatic impairment (TB > 3 to 10 x ULN and any AST).

Method of administration

VYLOY is for intravenous use. The recommended dose is administered by intravenous infusion over a minimum of 2 hours. VYLOY must not be administered as an intravenous push or bolus injection.

If VYLOY and fluoropyrimidine- and platinum-containing chemotherapy are administered on the same day, VYLOY must be administered first.

To help minimise potential adverse reactions, it is recommended that each infusion should be started at a slower rate than the initially calculated rate for the entire infusion, and gradually increased as tolerated during the course of the infusion (see Table 3).

If the infusion time exceeds the recommended storage time at room temperature (12 hours from end of preparation of infusion solution), the infusion bag must be discarded and a new infusion bag prepared to continue the infusion (see section 6.3 for recommended storage times).

Table 3. Infusion Rates Recommended for Each VYLOY Infusion

VYLOY Dose		**Infusion Rate**	
		First 30-60 minutes	**Remaining Infusion time**[b]
Single Loading Dose (Cycle 1, Day 1)[a]	800 mg/m^2	75 mg/m^2/hr	150-300 mg/m^2/hr
Maintenance Doses	600 mg/m^2 every 3 weeks or 400 mg/m^2 every 2 weeks	75 mg/m^2/hr or 50 mg/m^2/hr	150-300 mg/m^2/hr or 100-200 mg/m^2/hr

a. The cycle duration of VYLOY is determined based on the respective chemotherapy backbone (see section 5.1 Pharmacodynamic Properties).
b. In the absence of adverse reactions after 30-60 minutes, the infusion rate can be increased as tolerated.

Instructions for preparation and administration

Reconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of anticancer drugs.
2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
3. Calculate the recommended dose based on the patient's body surface area to determine the number of vials needed.
4. Reconstitute the vial by slowly adding 5.0 mL of Sterile Water For Injection (SWFI). If possible, direct the stream of SWFI along the walls of the vial and not directly onto the lyophilised powder. The reconstituted solution contains 20 mg/mL of VYLOY.
5. Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle. Visually inspect the solution until the bubbles are gone. **Do not shake the vial.**
6. Visually inspect the solution for particulate matter and discoloration. The reconstituted solution should be clear to slightly opalescent, colourless to slight yellow and free of visible particles. Discard any vial with visible particles or discoloration.
7. Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, refer to section 6.3 Shelf Life.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
9. Dilute VYLOY with 0.9% Sodium Chloride Injection. The infusion bag size should allow enough diluent to achieve a final concentration of 2 mg/mL VYLOY.

The diluted dosing solution of VYLOY is compatible with intravenous infusion bags composed of polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with either plasticiser [Di-(2-ethylhexyl) phthalate (DEHP) or Trioctyl trimellitate (TOTM)], ethylene propylene copolymer, ethylene-vinyl acetate (EVA) copolymer, PP and styrene-ethylene-butylene-styrene copolymer, or glass (bottle for administration use), and infusion tubing composed of PE, PVC with either plasticiser [DEHP, TOTM or Di(2-ethylhexyl) terephthalate], polybutadiene (PB), or elastomer modified PP with in-line filter membranes (pore size 0.2 µm) composed of polyethersulfone (PES) or polysulfone.

10. Mix diluted solution by gentle inversion. **Do not shake the bag.**
11. Visually inspect the infusion bag for any particulate matter prior to use. The diluted solution should be free of visible particles. Do not use the infusion bag if particulate matter is observed.
12. Product is for single use in one patient only. Discard any residue.

Administration

13. Do not co-administer other drugs through the same infusion line.

14. Immediately administer the infusion over a minimum of 2 hours through an intravenous line. Do not administer as an IV push or bolus.

No incompatibilities have been observed with closed system transfer device composed of PP, PE, stainless steel, silicone (rubber/oil/resin), polyisoprene, PVC or with plasticiser [TOTM], acrylonitrile-butadiene-styrene (ABS) copolymer, methyl methacrylate-ABS copolymer, thermoplastic elastomer, polytetrafluoroethylene, polycarbonate, PES, acrylic copolymer, polybutylene terephthalate, PB, or EVA copolymer. No incompatibilities have been observed with central port composed of silicone rubber, titanium alloy or PVC with plasticiser [TOTM].

In-line filters (pore size of 0.2 μm with materials listed above) are recommended to be used during administration.

15. If not administered immediately, see section 6.3 Shelf Life for storage of the prepared infusion bag.

4.3 CONTRAINDICATIONS

VYLOY is contraindicated in patients with known hypersensitivity to zolbetuximab or to any of the excipients in the formulation (see Section 6.1 – List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

Hypersensitivity reactions in patients treated with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy during clinical studies were characterised by anaphylactic reaction or drug hypersensitivity (see section 4.8 Adverse Effects).

Monitor patients during and after infusion with VYLOY (at least 2 hours, or longer if clinically indicated) for hypersensitivity reactions with symptoms and signs that are highly suggestive of anaphylaxis (e.g., urticaria, repetitive cough, wheeze and throat tightness/change in voice).

Hypersensitivity reactions should be managed according to the dose modifications as recommended in Table 2.

Infusion-related reactions

Infusion-related reactions (IRRs) have occurred during clinical studies with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy (see section 4.8 Adverse Effects).

Monitor patients for signs and symptoms of infusion-related reaction including nausea, vomiting, abdominal pain, salivary hypersecretion, pyrexia, chest discomfort, chills, back pain, cough and hypertension. These signs and symptoms are usually reversible with the interruption of the infusion.

Infusion-related reactions should be managed according to the dose modifications as recommended in Table 2.

Nausea and Vomiting

During clinical studies, nausea and vomiting were the most frequently observed gastrointestinal (GI) adverse reactions with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy treatment (see section 4.8 Adverse Effects).

Patients who experience severe vomiting may be at risk of GI haemorrhage when receiving VYLOY treatment. Monitor patients for vomiting that worsens and for signs and symptoms of GI haemorrhage during VYLOY therapy. Promptly evaluate and treat any suspected GI haemorrhage.

Nausea and vomiting occurred more often during the first cycle of treatment but decreased in incidence with subsequent cycles of treatment.

Prior to treatment with zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy, prescribers should evaluate the individual patient's risk of gastrointestinal toxicities. It is important to proactively manage nausea and vomiting to mitigate the potential risk of reduced efficacy due to reduced exposure to zolbetuximab and/or chemotherapy.

To prevent nausea and vomiting, pre-treatment with a combination of antiemetics is recommended prior to each infusion of VYLOY (see section 4.2 Dose and method of administration). During infusion, it is important to closely monitor patients and manage gastrointestinal toxicities by infusion interruption and/or infusion rate reduction to minimise the risk of severe adverse reactions or early treatment discontinuation.

During and after infusion, patients should be monitored and managed using standard of care, including antiemetics or fluid replacement, as clinically indicated.

Nausea and vomiting should be managed according to the dose modifications as recommended in Table 2.

Posterior Reversible Encephalopathy Syndrome (PRES)

There is the potential for patients treated with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy to develop signs and symptoms that are consistent with PRES which is a rare reversible, neurological disorder that can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of treatment in patients who develop PRES is recommended.

Use in renal impairment

No dose adjustment is required in patients with mild (CrCL ≥60 to <90 mL/min) or moderate (CrCL ≥30 to <60 mL/min) renal impairment (see section 5.2 Pharmacokinetic Properties). VYLOY has only been evaluated in a limited number of patients with severe (CrCL ≥15 to <30 mL/min) renal impairment.

Use in hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (TB ≤ ULN and AST > ULN, or TB > 1 to 1.5 x ULN and any AST) (see section 5.2 Pharmacokinetic Properties). VYLOY has only been evaluated in a limited number of patients with moderate hepatic impairment (TB > 1.5 to 3 x ULN and any AST) and has not been evaluated in patients with severe hepatic impairment (TB > 3 to 10 x ULN and any AST).

Use in the elderly

No dose adjustment is required in patients ≥65 years of age (see section 5.2 Pharmacokinetic Properties). Data for patients aged 75 years and older who received zolbetuximab are limited.

Paediatric use

The safety and efficacy of VYLOY in the paediatric population have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Zolbetuximab is not a cytokine modulator and there are no known effects of its mechanism of action on cytochrome P450 or drug transporters; therefore, no *in vitro* or *in vivo* drug-drug interaction or transporter studies have been conducted.

Based on a phase 2 study, coadministration of zolbetuximab with mFOLFOX6 did not show a clinically meaningful change in drug exposure of zolbetuximab, oxaliplatin, or 5-fluorouracil (5-FU). Therefore, no dose adjustment is required for zolbetuximab and mFOLFOX6 when used in combination.

This finding is also expected to be applicable to CAPOX, which contains oxaliplatin and capecitabine (a prodrug of 5-FU), therefore no dose adjustment is required for zolbetuximab and CAPOX when used in combination.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies have not been performed with VYLOY.

Use in pregnancy (Category B2)

There are no data on the use of VYLOY in pregnancy. In an embryo-foetal development toxicity study, where zolbetuximab was administered to pregnant mice during the period of organogenesis at doses up to 300 mg/kg (up to approximately 35 times the recommended human dose of 600 mg/m^2, based on AUC), zolbetuximab crossed the placental barrier and did not result in any external or visceral foetal abnormalities (malformations or variations). VYLOY should only be given during pregnancy if the benefit outweighs the potential risk.

Use in lactation

There are no data on the presence of zolbetuximab in human milk, the effects on the breastfed child, or the effects on milk production. It is known that antibodies (including IgG1) are excreted

in human milk and because of the potential for serious adverse effects in a breastfed child, breastfeeding is not recommended during treatment with VYLOY.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies with VYLOY and the effects on the ability to drive or use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of zolbetuximab was evaluated in the integrated safety population from two phase 2 studies (FAST, ILUSTRO) and two phase 3 studies (SPOTLIGHT, GLOW) in 631 patients who received at least one dose of zolbetuximab 800 mg/m^2 as a loading dose followed by 600 mg/m^2 maintenance doses every 3 weeks in combination with fluoropyrimidine and platinum-containing chemotherapy. The median duration of exposure to zolbetuximab was 174 days (range: 1 to 1791 days).

Serious adverse reactions occurred in 45% of patients treated with zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy. The most common serious adverse reactions (≥2%) were vomiting (6.8%) and nausea (4.9%).

Thirty-seven percent of patients permanently discontinued zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy for adverse reactions; the most common adverse reactions (≥2%) leading to dose discontinuation were vomiting (5.4%) and nausea (4.3%).

Adverse reactions leading to dose interruption of zolbetuximab and/or fluoropyrimidine and/or platinum-containing chemotherapy occurred in 73% of patients; the most common adverse reactions (≥2%) leading to dose interruption were vomiting (29.3%), nausea (28.4%) and decreased appetite (3.6%).

The most common adverse reactions (≥2%) leading to dose rate reduction of the zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy infusion were nausea (9.7%) and vomiting (7.8%).

Tabulated summary of adverse reactions

Adverse reactions observed during clinical studies are listed in this section by frequency category. Frequency categories are defined as follows: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The most common adverse events (all grade frequency ≥15%) are presented in Table 4.

Table 4. Most Common Adverse Events (≥%15)

System Organ Class	Preferred Term	Integrated Safety Summary[a,b]			
		VYLOY with fluoropyrimidine and platinum-containing chemotherapy n=631		Placebo with fluoropyrimidine and platinum-containing chemotherapy n=611	
		Any Grade	Grade ≥3	Any Grade	Grade ≥3
		n (%)	n (%)	n (%)	n (%)
Metabolism and nutrition disorders	Hypoalbuminaemia[c]	108 (17.1)	20 (3.2)	57 (9.3)	7 (1.1)
	Decreased appetite[c]	265 (42.0)	35 (5.5)	201 (32.9)	14 (2.3)
Gastrointestinal disorders	Vomiting[c]	422 (66.9)	86 (13.6)	225 (36.8)	29 (4.7)
	Diarrhoea	219 (34.7)	31 (4.9)	243 (39.8)	31 (5.1)
	Abdominal pain	132 (20.9)	18 (2.9)	153 (25.0)	13 (2.1)
	Constipation	151 (23.9)	3 (0.5)	172 (28.2)	4 (0.7)
	Nausea[c]	487 (77.2)	73 (11.6)	360 (58.9)	29 (4.7)
Blood and lymphatic system disorders	Neutropenia	194 (30.7)	127 (20.1)	158 (25.9)	89 (14.6)
	Anaemia	237 (37.6)	64 (10.1)	228 (37.3)	59 (9.7)
Nervous system disorders	Peripheral sensory neuropathy	176 (27.9)	16 (2.5)	180 (29.5)	21 (3.4)
General disorders and administration site conditions	Pyrexia	110 (17.4)	4 (0.6)	90 (14.7)	1 (0.2)
	Asthenia	130 (20.6)	30 (4.8)	114 (18.7)	12 (2.0)
	Fatigue	150 (23.8)	31 (4.9)	151 (24.7)	27 (4.4)
Investigations	White blood cell count decreased	104 (16.5)	13 (2.1)	88 (14.4)	27 (4.4)
	Neutrophil count decreased	179 (28.4)	102 (16.2)	152 (24.9)	94 (15.4)
	Aspartate aminotransferase increased	121 (19.2)	13 (2.1)	133 (21.8)	17 (2.8)
	Alanine aminotransferase increased	90 (14.3)	7 (1.1)	112 (18.3)	18 (2.9)
	Platelet count decreased	106 (16.8)	23 (3.6)	111 (18.2)	27 (4.4)
	Weight decreased	138 (21.9)	16 (2.5)	105 (17.2)	7 (1.1)

a. Preferred terms in MedDRA (v25.0).
b. The above-mentioned listed adverse events have been observed during clinical studies of VYLOY (FAST, ILUSTRO, SPOTLIGHT, GLOW data cutoffs 31Jan2019, 03May2021, 08Sep2023, 12Jan2024, respectively).
c. The treatment-emergent adverse event is considered causally related (ADR) to zolbetuximab treatment.

Less common adverse reactions (all grade frequency <15% in the VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy arm) observed during clinical studies are listed below by frequency category.

Immune system disorders
Common: Drug hypersensitivity
Uncommon: Anaphylactic reaction

Injury, poisoning and procedural complications
Common: Infusion related reaction

Gastrointestinal disorders
Common: Salivary hypersecretion

General disorders and administration site conditions
Very common: Oedema peripheral

Selected Adverse Reactions

Hypersensitivity reactions

In the integrated safety analysis, all grade anaphylactic reaction or drug hypersensitivity occurred in the VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy arm at a frequency of 0.5% (3/631) and 1.6% (10/631), respectively. In the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm, the rates were 0.8% (5/611) and 1.6% (10/611), respectively.

Severe (Grade ≥ 3) anaphylactic reaction or drug hypersensitivity occurred at a similar frequency in the VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.5% (3/631), 0.2% (1/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.3% (2/611), 0.2% (1/611)]. The median time to onset of anaphylactic reaction or drug hypersensitivity with zolbetuximab and/or with fluoropyrimidine and platinum containing chemotherapy was 22 days or 113 days, respectively.

Three patients (0.5%) permanently discontinued VYLOY and/or fluoropyrimidine and platinum-containing chemotherapy due to anaphylactic reaction. Dose interruption of VYLOY and/or fluoropyrimidine and platinum-containing chemotherapy was experienced due to drug hypersensitivity in six patients (1.0%). The infusion rate was reduced for VYLOY and/or fluoropyrimidine and platinum-containing chemotherapy in one patient (0.2%) due to drug hypersensitivity.

Infusion related reactions

In the integrated safety analysis, all grade IRR occurred in the VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy arm at 3.2% (20/631) compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm at 1.1% (7/611). Severe (Grade ≥ 3) IRR occurred more frequently in the VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.5% (3/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0% (0/611)]. The median time to onset of infusion-related reaction with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy was 22 days.

An IRR led to permanent discontinuation of VYLOY and/or fluoropyrimidine and platinum-containing chemotherapy in 4 (0.6%) patients and dose interruption in 10 (1.6%) patients. The infusion rate was reduced for VYLOY and/or fluoropyrimidine and platinum-containing chemotherapy in 2 patients (0.3%) due to an IRR.

Nausea and vomiting

In the integrated safety analysis, all grade nausea or vomiting occurred more frequently in the VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy arm [77.2% (487/631), 66.9% (422/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [58.9% (360/611), 36.8% (225/611)]. Severe (Grade ≥ 3) nausea or vomiting in the VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy and placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arms occurred at the following frequencies: nausea [11.6% (73/631); 4.7% (29/611)] or vomiting [13.6% (86/631); 4.7% (29/611)]. The median time to onset of nausea or vomiting with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy was 1 day or 1 day, respectively.

Nausea led to permanent discontinuation of VYLOY and/or fluoropyrimidine and platinum-containing chemotherapy in 27 (4.3%) patients and dose interruption in 179 (28.4%) patients. Vomiting led to permanent discontinuation of VYLOY and/or fluoropyrimidine and platinum-containing chemotherapy in 34 (5.4%) patients and dose interruption in 185 (29.3%) patients. The infusion rate was reduced for VYLOY and/or fluoropyrimidine and platinum-containing chemotherapy in 61 patients (9.7%) due to nausea and in 49 patients (7.8%) due to vomiting.

Immunogenicity

In an approximately 30-month treatment period of clinical studies SPOTLIGHT AND GLOW, the incidence of treatment emergent anti- zolbetuximab antibody formation was 4.4% [21 of 479 total VYLOY-treated patients who were tested for anti-drug antibodies (ADAs)]. Because of the low occurrence of immunogenicity, the effect of these antibodies on the pharmacokinetics, safety and/or effectiveness of VYLOY is unknown.

Reporting suspected adverse effects

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

4.9 OVERDOSE

In case of overdose, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered, as appropriate.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates.

ATC code: L01FX31

Mechanism of action

Zolbetuximab is a genetically engineered, highly purified chimeric (mouse/human IgG1) monoclonal antibody directed against the tight junction molecule CLDN18.2. Nonclinical data suggest zolbetuximab binds selectively to cell lines transfected with CLDN18.2 or those that endogenously express CLDN18.2. Zolbetuximab depletes CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Cytotoxic drugs were shown to increase CLDN18.2 expression on human cancer cells and to improve zolbetuximab -induced ADCC and CDC activities. In immunocompetent mice tumour models, zolbetuximab demonstrated an antitumour effect on CLDN18.2 expressing tumours injected subcutaneously and a combination of zolbetuximab with chemotherapy showed a more potent effect than zolbetuximab or chemotherapy alone.

Pharmacodynamic effects

Zolbetuximab doses of 800/600 mg/m^2 every 3 weeks were evaluated in clinical studies, with doses of 800/400 mg/m^2 every 2 weeks evaluated using modeling and simulation.
Based on the exposure-response analyses of efficacy and safety in patients with locally advanced unresectable or metastatic HER2-negative gastric or GOJ adenocarcinoma whose tumours are CLDN18.2 positive, there are no anticipated clinically significant differences in efficacy or safety between VYLOY doses of 800/400 mg/m^2 every 2 weeks and 800/600 mg/m^2 every 3 weeks.

Concentration-QTc interval

At the recommended dosage, VYLOY had no clinically meaningful effect on QTc prolongation.

Clinical trials

Gastric or GOJ Adenocarcinoma

SPOTLIGHT (8951-CL-0301) and GLOW (8951-CL-0302)

The safety and efficacy of VYLOY in combination with chemotherapy was evaluated in two phase 3, double-blind, randomised, multicentre studies – SPOTLIGHT and GLOW. These two phase 3 studies enrolled 1072 patients with locally advanced unresectable or metastatic gastric or GOJ adenocarcinoma whose tumours were CLDN18.2 positive and HER2-negative. CLDN18.2 positivity (defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 staining) was determined by immunohistochemistry on gastric or GOJ tumour tissue specimens from all patients with the VENTANA CLDN18 (43-14A) RxDx Assay performed in a central laboratory.

In each phase 3 study, patients were randomised 1:1 to receive either zolbetuximab in combination with chemotherapy (n=537) or placebo in combination with chemotherapy (n=535). Zolbetuximab was administered intravenously at a loading dose of 800 mg/m^2 (Day 1 of cycle 1) followed by a maintenance dose of 600 mg/m^2 every 3 weeks in combination with mFOLFOX6 (SPOTLIGHT) or CAPOX (GLOW).

Patients were excluded from the studies if they had a complete or partial gastric outlet syndrome, positive test for human immunodeficiency virus (HIV) infection or known active hepatitis B or C infection, significant cardiovascular disease (e.g., congestive heart failure per New York Heart Association Class III or IV, history of significant ventricular arrhythmias, QTc interval >450 msec for males; >470 msec for females) or history of central nervous system metastases.

Patients in the SPOTLIGHT study received up to 12 treatments (4 cycles) of mFOLFOX6 [oxaliplatin 85 mg/m^2, folinic acid (leucovorin or local equivalent) 400 mg/m^2, fluorouracil 400 mg/m^2 given as a bolus and fluorouracil 2400 mg/m^2 given as a continuous infusion] administered on Days 1, 15 and 29 of a 42-day cycle. After 12 treatments, patients were allowed to continue treatment with zolbetuximab, 5-FU and folinic acid (leucovorin or local equivalent) at the discretion of the investigator, until progression of disease or unacceptable toxicity.

Patients in the GLOW study received up to 8 treatments (8 cycles) of CAPOX administered on Day 1 (oxaliplatin 130 mg/m^2) and on Days 1 to 14 (capecitabine 1000 mg/m^2) of a 21-day cycle. After 8 treatments of oxaliplatin, patients were allowed to continue treatment of zolbetuximab and capecitabine at the discretion of the investigator, until progression of disease or unacceptable toxicity.

For both SPOTLIGHT and GLOW, the primary efficacy outcome was progression-free survival (PFS) as assessed per RECIST v1.1 by an independent review committee (IRC). The key secondary efficacy outcome for both studies was overall survival (OS). Other secondary efficacy outcomes were objective response rate (ORR) and duration of response (DOR) as assessed per RECIST v1.1 by IRC.

Table 5 summarises the primary analysis (final PFS, interim OS) baseline characteristics for SPOTLIGHT and GLOW.

Table 5. Baseline characteristics in SPOTLIGHT and GLOW (primary analysis)

	SPOTLIGHT		GLOW	
Category	**VYLOY with mFOLFOX6 n=283**	**Placebo with mFOLFOX6 n=282**	**VYLOY with CAPOX n=254**	**Placebo with CAPOX n=253**
Age (years)				
Median age (range)	62 (27 to 83)	60 (20 to 86)	61 (22 to 82)	59 (21 to 83)
≥18 to ≤64 (%)	60	62	66	68
≥65 (%)	40	38	34	32
Race (%)				
White	54	53	37	36
Asian	37	38	63	64
American Indian or Alaskan	3	3	0	0
Black or African American	2	1	0	0
Other	4	5	0	0
Gender (%)				
Male	62	62	63	62
Female	38	38	37	38
ECOG performance status				
0 (%)	45	41	43	43
1 (%)	55	59	57	57
Missing data (n)	4	4	1	3
Mean body surface area (m^2), (range)	1.7 (1.2 to 2.4)	1.7 (1.1 to 2.5)	1.7 (1.2 to 2.3)	1.7 (1.1 to 2.3)
Median time from diagnosis (days), (range)	56 (2 to 3010)	56 (7 to 5366)	44 (12 to 2396)	44 (2 to 6010)
Tumour location				
Distal (%)	39	42	39	38
Proximal (%)	37	30	35	37
Unknown (%)	24	28	26	25
Missing (n)	3	1	0	0
Tumour types				
Diffuse (%)	29	42	34	40
Intestinal (%)	25	24	14	16
Other (%)	18	15	13	11
Mixed (%)	11	5	8	8
Unknown (%)	17	14	30	25
Missing (n)	1	4	1	0

In the final PFS and interim OS analyses, zolbetuximab in combination with mFOLFOX6 (SPOTLIGHT) or CAPOX (GLOW) demonstrated a statistically significant improvement in PFS and OS compared with placebo in combination with mFOLFOX6 or CAPOX.

Table 6, Figures 1 to 4 summarise the primary analysis efficacy results in PFS and the final analysis efficacy in OS for SPOTLIGHT and GLOW.

Table 6. Efficacy results in SPOTLIGHT and GLOW

Endpoint	SPOTLIGHT[a]		GLOW[b]	
	VYLOY with mFOLFOX6 n=283	**Placebo with mFOLFOX6 n=282**	**VYLOY with CAPOX n=254**	**Placebo with CAPOX n=253**
Progression-free survival				
Number (%) of patients with events	146 (51.6)	167 (59.2)	137 (53.9)	172 (68.0)
Median in months (95% CI)[c]	10.6 (8.9, 12.5)	8.7 (8.2, 10.3)	8.2 (7.5, 8.8)	6.8 (6.1, 8.1)
Hazard ratio (95% CI)[d,e]	0.751 (0.598, 0.942)		0.687 (0.544, 0.866)	
1-sided p-value[d,f]	0.0066		0.0007	
Overall survival				
Number (%) of patients with events	197 (69.6)	217 (77.0)	180 (70.9)	207 (81.8)
Median in months (95% CI)[c]	18.2 (16.1, 20.6)	15.6 (13.7, 16.9)	14.3 (12.1, 16.4)	12.2 (10.3, 13.7)
Hazard ratio (95% CI)[d,e]	0.784 (0.644, 0.954)		0.763 (0.622, 0.936)	
1-sided p-value[b,d]	0.0053		0.0118	
Objective response rate (ORR), Duration of response (DOR)				
ORR (%) (95% CI)[g]	48.1 (42.1, 54.1)	47.5 (41.6, 53.5)	42.5 (36.4, 48.9)	39.1 (33.1, 45.4)
DOR Median in months (95% CI)[g]	9.0 (7.5, 10.4)	8.1 (6.5, 11.4)	6.3 (5.4, 8.3)	6.1 (4.4, 6.3)

a. PFS: SPOTLIGHT data cut-off: 09-Sep-2022, median follow-up time of zolbetuximab in combination with mFOLFOX6 arm was 12.9 months.
OS, ORR, DOR: SPOTLIGHT data cut-off: 08-Sep-2023, median follow-up time of zolbetuximab in combination with mFOLFOX6 arm for OS was 33.3 months.

b. PFS: GLOW data cut-off: 07-Oct-2022, median follow-up time of zolbetuximab in combination with CAPOX arm 12.6 months.
OS, ORR, DOR: GLOW data cut-off: 12-Jan-2024, median follow-up time of zolbetuximab in combination with CAPOX arm for OS was 31.7 months.

c. Based on Kaplan-Meier estimate.

d. Stratification factors were region, number of metastatic sites, prior gastrectomy from IRT.

e. Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites, prior gastrectomy as the explanatory variables.

f. Based on 1-sided log-rank test.

g. Based on IRC assessment and unconfirmed responses.

Figure 1. Kaplan Meier plot of progression free survival, SPOTLIGHT (primary analysis)

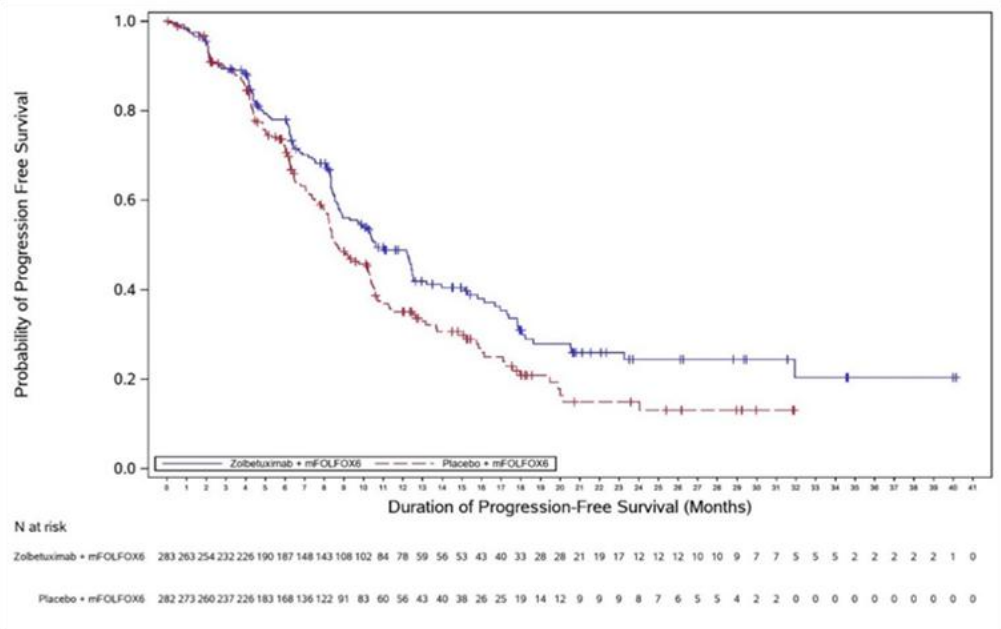


Figure 2. Kaplan Meier plot of progression-free survival, GLOW (primary analysis)

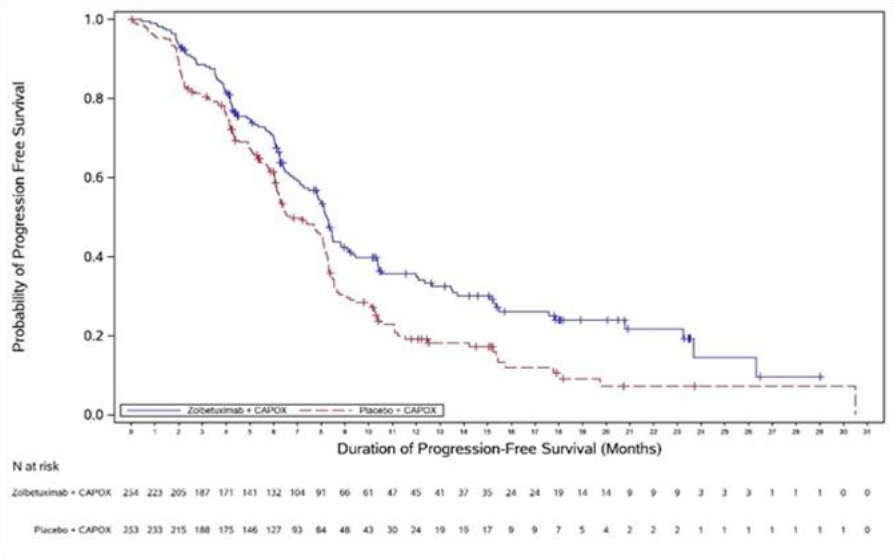


Figure 3. Kaplan Meier plot of overall survival, SPOTLIGHT (final analysis)

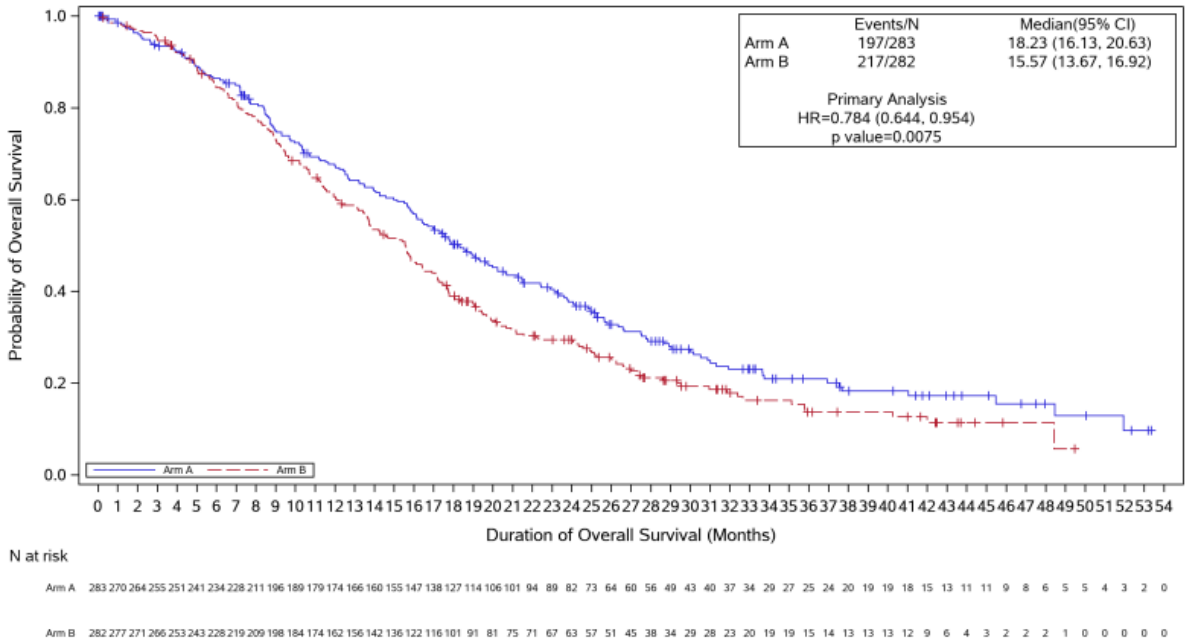
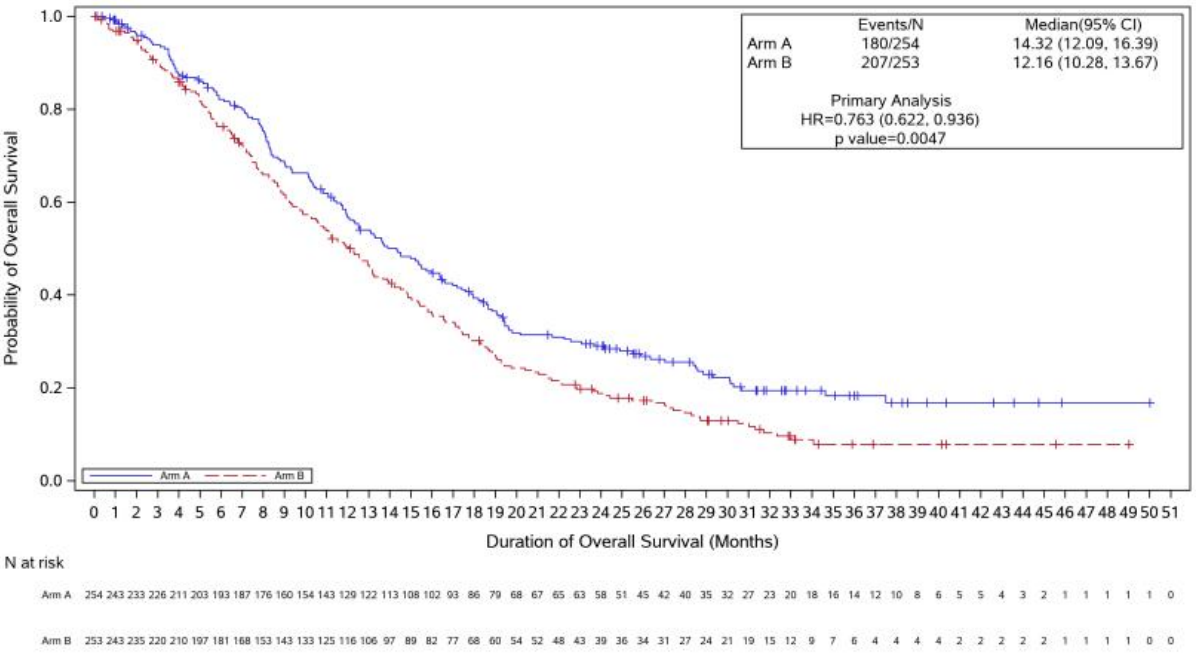


Figure 4. Kaplan Meier plot of overall survival, GLOW (final analysis)



5.2 PHARMACOKINETIC PROPERTIES

Following intravenous administration, VYLOY exhibited dose-proportional pharmacokinetics at doses ranging from 33 mg/m^2 to 1000 mg/m^2. When administered at 800/600 mg/m^2 every 3 weeks, steady state was achieved by 18 weeks with a mean (SD) C_{max} and AUC_{tau} at 425 (91) µg/mL and 3359 (1254) day•µg/mL, respectively.

Distribution

The estimated mean steady state volume of distribution of VYLOY was 16.4 L.

Metabolism

VYLOY is expected to be catabolised into small peptides and amino acids.

Excretion

The estimated mean clearance (CL) and $t_{1/2}$ of VYLOY was 0.0150 L/h and 43.6 d, respectively.

Pharmacokinetic Characteristics in Special Populations

Elderly

Population pharmacokinetic analysis indicates that age [range: 22 to 83 years; 32.2% (230/714) were >65 years, 5.0% (36/714) were >75 years] did not have a clinically meaningful effect on the pharmacokinetics of VYLOY.

Race and gender

Based on the population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of VYLOY were identified based on gender [62.3% male, 37.7% female] or race [50.1% White, 42.2% Asian, 4.2% Missing, 2.7% Others, and 0.8% Black].

Renal impairment

Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GOJ adenocarcinomas, no clinically significant differences in the pharmacokinetics of VYLOY were identified in patients with mild (CrCL ≥60 to <90 mL/min; n=298) to moderate (CrCL ≥30 to <60 mL/min; n=109) renal impairment based on CrCL estimated by the C-G formula. VYLOY has only been evaluated in a limited number of patients with severe renal impairment (CrCL ≥15 to <30 mL/min; n=1).

Hepatic impairment

Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GOJ adenocarcinomas, no clinically significant differences in the pharmacokinetics of VYLOY were identified in patients with mild hepatic impairment (TB ≤ ULN and AST > ULN, or TB > 1 to 1.5 x ULN and any AST; n=108). VYLOY has only been evaluated in a limited number of patients with moderate hepatic impairment (TB > 1.5 to 3 x ULN and any AST; n=4) and has not been evaluated in patients with severe hepatic impairment (TB > 3 to 10 x ULN and any AST).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Arginine
Phosphoric Acid
Sucrose
Polysorbate 80

6.2 INCOMPATIBILITIES

Do not co-administer other drugs through the same infusion line.

6.3 SHELF LIFE

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

Reconstituted vial
Reconstituted vials may be stored at room temperature for up to 6 hours. Do not freeze. Do not expose to direct sunlight. Discard unused vials with reconstituted solution beyond the recommended storage time.

Prepared infusion bag
The prepared infusion bag should be administered immediately. If not administered immediately, the prepared infusion bag should be stored:

- under refrigeration at 2°C to 8°C for no longer than 24 hours including infusion time from the end of the preparation of the infusion bag. Do not freeze.
- at room temperature for no longer than 12 hours including infusion time from when the prepared infusion bag is removed from the refrigerator. Do not expose to direct sunlight.

Discard unused prepared infusion bags beyond the recommended storage time.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2˚C to 8˚C (Refrigerate. Do not freeze).

6.5 NATURE AND CONTENTS OF CONTAINER

Clear Type I 20 mL glass vial with European blow-back feature

Gray bromobutyl rubber stopper with ethylene tetrafluoroethylene film

20 mm aluminum seal with a green cap

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Zolbetuximab is a genetically engineered, highly purified chimeric (mouse/human IgG1) monoclonal antibody directed against the tight junction molecule CLDN18.2.

Chemical structure

VYLOY is a recombinant chimeric (mouse / human) monoclonal antibody composed of variable regions derived from mouse anti-human claudin-18 splice variant 2 monoclonal antibody and constant regions derived from human IgG1. VYLOY is a glycoprotein composed of 2 heavy chains (γ1-chains) consisting of 448 amino acid residues each and 2 light chains (κ-chains) consisting of 220 amino acid residues each.

VYLOY is a heterogeneous mixture of related species with variable post-translational modifications. Asn298 in the heavy chain constitutes the single consensus *N*-glycosylation site, and the typical glycan is biantennary, core fucosylated and variably galactosylated with the most abundant species having no galactose residues. The molecular formula and molecular weight of VYLOY excluding glycan are presented in Table .

Table 7. Chemical Properties of VYLOY (excluding glycan)

Molecular Formula	$C_{6522}H_{10036}N_{1720}O_{2054}S_{44}$
Molecular Weight (average)	146,815 Da

CAS number

1496553-00-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

17 March 2025

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	New Product Information