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

Vyloy 100 mg powder for concentrate for solution for infusion.
Vyloy 300 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vyloy 100 mg powder for concentrate for solution for infusion
Each vial of powder for concentrate for solution for infusion contains 100 mg zolbetuximab.

Vyloy 300 mg powder for concentrate for solution for infusion
Each vial of powder for concentrate for solution for infusion contains 300 mg zolbetuximab.

After reconstitution, each mL of solution contains 20 mg of zolbetuximab.

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

Excipient with known effect

Each mL of concentrate contains 0.21 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised powder.

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 HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive (see section 4.2).

4.2 Posology and method of administration

Treatment should be prescribed, initiated and supervised by a physician experienced in the use of anti-cancer therapies. Resources for the management of hypersensitivity reactions and/or anaphylactic reactions should be available.

Patient selection

Eligible patients should have CLDN18.2 positive tumour status defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining, assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.

Posology

Prior to administration

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

Prior to each infusion of zolbetuximab, patients should be pre-medicated with a combination of antiemetics (e.g., NK-1 receptor blockers and 5-HT3 receptor blockers, as well as other medicinal products as indicated).

Pre-medication with a combination of antiemetics is important for the management of nausea and vomiting to prevent early treatment discontinuation of zolbetuximab (see section 4.4). Pre-medication with systemic corticosteroids per local treatment guidelines may also be considered particularly before the first infusion of zolbetuximab.

Recommended dose

The recommended dose should be calculated according to body surface area (BSA) for the zolbetuximab loading dose and maintenance doses as provided in Table 1.

Table 1. Recommended zolbetuximab dose based on BSA

Single loading dose	Maintenance doses	Duration of therapy
On Cycle 1, Day 1[a], 800 mg/m^2 intravenously Administer zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1).[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 Administer zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1).[b]	Until disease progression or unacceptable toxicity.

a. The cycle duration of zolbetuximab is determined based on the respective chemotherapy backbone (see section 5.1).
b. Refer to the fluoropyrimidine- or platinum-containing chemotherapy prescribing information regarding the dosing information for chemotherapy.

Dose modifications

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

Table 2. Dose modifications for zolbetuximab

Adverse reaction	Severity[a]	Dose modification
Hypersensitivity reactions	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 with antihistamines and administer per the infusion rates in Table 3.
Infusion related reaction	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 with antihistamines and administer per the infusion rates in Table 3.
Nausea	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	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 (see section 4.4 for patient monitoring recommendations).

Special populations

Elderly

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

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. No dose recommendation has been established in patients with severe renal impairment (CrCL ≥15 to <30 mL/min) (see section 5.2).

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 × ULN and any AST). No dose recommendation has been established in patients with moderate (TB >1.5 to 3 × ULN and any AST) or severe (TB >3 to 10 × ULN and any AST) hepatic impairment (see section 5.2).

Paediatric population

There is no relevant use of zolbetuximab in the paediatric population in the treatment of gastric or gastro-oesophageal junction adenocarcinoma.

Method of administration

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

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

To help minimise potential adverse reactions, it is recommended that each infusion is started at a slower rate for 30-60 minutes, 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 (≤ 25 °C for 8 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 zolbetuximab infusion

Zolbetuximab 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 zolbetuximab is determined based on the respective chemotherapy backbone (see section 5.1).
b. In the absence of adverse reactions after 30-60 minutes, the infusion rate can be increased as tolerated.

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

Hypersensitivity reactions

Hypersensitivity reactions, including anaphylactic reaction and drug hypersensitivity, occurred in patients treated with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy during clinical studies (see section 4.8).

Patients should be monitored during and after infusion with zolbetuximab (at least 2 hours, or longer if clinically indicated) for hypersensitivity reactions with symptoms and signs that are highly suggestive of anaphylaxis (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 zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy (see section 4.8).

Patients should be monitored for signs and symptoms of infusion-related reactions 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 adverse reactions with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy (see section 4.8).

To prevent nausea and vomiting, pre-treatment with a combination of antiemetics is recommended prior to each infusion of zolbetuximab (see section 4.2).

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.

Mitigation measures before initiating treatment with zolbetuximab

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 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 zolbetuximab. During infusion, it is important to closely monitor patients and manage gastrointestinal toxicities by infusion interruption and/or infusion rate reduction to minimize 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.

Patients excluded from clinical studies

Patients were excluded from clinical 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.

Excipient information

This medicinal product contains 1.05 mg and 3.15 mg of polysorbate 80 in each 100 mg and 300 mg vial, respectively. Polysorbates may cause allergic reactions.

This medicinal product does not contain sodium, however, sodium chloride 9 mg/mL (0.9%) solution for infusion is used for the dilution of zolbetuximab prior to administration and this should be taken into consideration in the context of the daily sodium intake of the patient.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with zolbetuximab. Since zolbetuximab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

As a precautionary measure, women of childbearing potential should be advised to use effective contraception to prevent pregnancy during treatment.

Pregnancy

There are no data on the use of zolbetuximab in pregnant women. No adverse effects were observed in an animal reproductive and developmental study with intravenous administration of zolbetuximab to pregnant mice during organogenesis (see section 5.3). Zolbetuximab should only be given to a pregnant woman if the benefit outweighs the potential risk.

Breast-feeding

There are no data on the presence of zolbetuximab in human milk, the effects on the breast-fed child, or the effects on milk production. Since it is known that antibodies can be excreted in human milk, and because of the potential for serious adverse reactions in a breast-fed child, breast-feeding is not recommended during treatment with zolbetuximab.

Fertility

Studies to evaluate the effect of zolbetuximab on fertility have not been performed. Thus, the effect of zolbetuximab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Zolbetuximab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions with zolbetuximab were nausea (77.2%), vomiting (66.9%), decreased appetite (42%), neutropenia (30.7%), neutrophil count decreased (28.4%), weight decreased (21.9%), pyrexia (17.4%), hypoalbuminaemia (17.1%), oedema peripheral (13.9%), hypertension (9%), dyspepsia (7.8%), chills (5.2%), salivary hypersecretion (3.8%), infusion related reaction (3.2%) and drug hypersensitivity (1.6%).

Serious adverse reactions occurred in 45% of patients treated with zolbetuximab. The most common serious adverse reactions were vomiting (6.8%), nausea (4.9%), and decreased appetite (1.9%).

Twenty percent of patients permanently discontinued zolbetuximab for adverse reactions; the most common adverse reactions leading to dose discontinuation were vomiting (3.8%) and nausea (3.3%).

Adverse reactions leading to dose interruption of zolbetuximab occurred in 60.9% of patients; the most common adverse reactions leading to dose interruption were vomiting (26.6%), nausea (25.5%), neutropenia (9.8%), neutrophil count decreased (5.9%), hypertension (3.2%), chills (2.2%), infusion related reaction (1.6%), decreased appetite (1.6%) and dyspepsia (1.1%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on two phase 2 studies and two phase 3 studies 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. Patients were exposed to zolbetuximab for a median duration of 174 days (range: 1 to 1791 days).

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.

Table 4. Adverse reactions

MedDRA System organ class	Adverse reaction	Frequency category
Blood and lymphatic system disorders	Neutropenia	Very common
	Neutrophil count decreased	
Immune system disorders	Drug hypersensitivity	Common
	Anaphylactic reaction	Uncommon
Metabolism and nutrition disorders	Hypoalbuminaemia	Very common
	Decreased appetite	
Vascular disorders	Hypertension	Common
Gastrointestinal disorders	Vomiting	Very common
	Nausea	
	Dyspepsia	Common
	Salivary hypersecretion	
General disorders and administration site conditions	Pyrexia	Very common
	Oedema peripheral	
	Chills	Common
Investigations	Weight decreased	Very common
Injury, poisoning and procedural complications	Infusion related reaction	Common

Description of selected adverse reactions

Hypersensitivity reactions

In the integrated safety analysis, all grade anaphylactic reaction and drug hypersensitivity occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 0.5% and 1.6%, respectively.

Severe (Grade 3) anaphylactic reaction and drug hypersensitivity occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 0.5% and 0.2%.

Anaphylactic reaction led to permanent discontinuation of zolbetuximab in 0.3% of patients. Dose interruption of zolbetuximab was experienced due to drug hypersensitivity in 0.3% of patients. The infusion rate was reduced for zolbetuximab or fluoropyrimidine and platinum-containing chemotherapy in 0.2% of patients due to drug hypersensitivity.

Infusion related reaction

In the integrated safety analysis, all grade IRR occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 3.2%.

Severe (Grade 3) IRR occurred in 0.5% of patients treated with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy.

An IRR led to permanent discontinuation of zolbetuximab in 0.5% of patients, and dose interruption in 1.6% of patients. The infusion rate was reduced for zolbetuximab or fluoropyrimidine and platinum-containing chemotherapy in 0.3% of patients due to an IRR.

Nausea and vomiting

In the integrated safety analysis, all grade nausea and vomiting occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 77.2% and 66.9%, respectively. Nausea and vomiting occurred more often during the first cycle of treatment but decreased in incidence with subsequent cycles of treatment. The median time to onset of nausea and vomiting was 1 day each with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy. The median duration of nausea and vomiting was 3 days and 1 day, respectively, with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy.

Severe (Grade 3) nausea and vomiting occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 11.6% and 13.6%.

Nausea led to permanent discontinuation of zolbetuximab in 3.3% of patients, and dose interruption in 25.5% of patients. Vomiting led to permanent discontinuation of zolbetuximab in 3.8% of patients, and dose interruption in 26.6% of patients. The infusion rate was reduced for zolbetuximab or fluoropyrimidine and platinum-containing chemotherapy in 9.7% of patients due to nausea and in 7.8% of patients due to vomiting.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX31

Mechanism of action

Zolbetuximab is a 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 medicinal products were shown to increase CLDN18.2 expression on human cancer cells and to improve zolbetuximab-induced ADCC and CDC activities.

Pharmacodynamic effects

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

Immunogenicity

Based on a pooled analysis of data from two phase 3 studies, the overall immunogenicity incidence was 9.5% (46 of 485 total patients treated with zolbetuximab 800/600 mg/m² every 3 weeks in combination with mFOLFOX6/CAPOX were tested positive for anti-drug antibodies [ADAs]). Because of the low occurrence of ADAs, the effect of these antibodies on the pharmacokinetics, safety and/or effectiveness of zolbetuximab is unknown.

Clinical efficacy and safety

Gastric or GEJ adenocarcinoma

SPOTLIGHT (8951-CL-0301) and GLOW (8951-CL-0302)
The safety and efficacy of zolbetuximab in combination with chemotherapy was evaluated in two phase 3, double-blind, randomised, multicentre studies that enrolled 1072 patients whose tumours were CLDN18.2 positive, HER2-negative, with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. CLDN18.2 positivity (defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 staining) was determined by immunohistochemistry on gastric or GEJ tumour tissue specimens from all patients with the VENTANA CLDN18 (43-14A) RxDx Assay performed in a central laboratory.

Patients were randomised 1:1 to receive either zolbetuximab in combination with chemotherapy (n=283 in SPOTLIGHT, n=254 in GLOW) or placebo in combination with chemotherapy (n=282 in SPOTLIGHT, n=253 in GLOW). Zolbetuximab was administered intravenously at a loading dose of 800 mg/m^2 (Day 1 of cycle 1) followed by maintenance doses of 600 mg/m^2 every 3 weeks in combination with either mFOLFOX6 (oxaliplatin, folinic acid and fluorouracil), or CAPOX (oxaliplatin and capecitabine).

Patients in the SPOTLIGHT study received between 1-12 treatments 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-fluorouracil 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 between 1-8 treatments 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.

Baseline characteristics were generally similar between studies, except for the proportion of Asian versus non-Asian patients in each study.

In the SPOTLIGHT study, the median age was 61 years (range: 20 to 86); 62% were male; 53% were Caucasian, 38% were Asian; 31% were from Asia and 69% were not from Asia. Patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (43%) or 1 (57%). Patients had a mean body surface area of 1.7 m^2 (range: 1.1 to 2.5). The median time from diagnosis was 56 days (range: 2 to 5366); 36% of tumour types were diffuse, 24% were intestinal; 76% had gastric adenocarcinoma, 24% had GEJ adenocarcinoma; 16% had locally advanced disease and 84% had metastatic disease.

In the GLOW study, the median age was 60 years (range: 21 to 83); 62% were male; 37% were Caucasian, 63% were Asian; 62% were from Asia and 38% were not from Asia. Patients had a baseline ECOG performance status of 0 (43%) or 1 (57%). Patients had a mean body surface area of 1.7 m^2 (range: 1.1 to 2.3). The median time from diagnosis was 44 days (range: 2 to 6010); 37% of tumour types were diffuse, 15% were intestinal; 84% had gastric adenocarcinoma, 16% had GEJ adenocarcinoma; 12% had locally advanced disease and 88% had metastatic disease.

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 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.

In the primary analysis (final PFS and interim OS), the SPOTLIGHT study demonstrated a statistically significant benefit in PFS (as assessed by IRC) and OS for patients who received zolbetuximab in combination with mFOLFOX6 compared with patients who received placebo in combination with mFOLFOX6 treatment. The PFS HR was 0.751 (95% CI: 0.598, 0.942; 1-sided P = 0.0066) and the OS HR was 0.750 (95% CI: 0.601, 0.936; 1-sided P = 0.0053).

The updated PFS and final OS analysis for SPOTLIGHT are presented in table 5 and Figures 1-2 show the Kaplan- Meier curves.

In the primary analysis (final PFS and interim OS), the GLOW study demonstrated a statistically significant benefit in PFS (as assessed by IRC) and OS for patients who received zolbetuximab in combination with CAPOX compared with patients who received placebo in combination with CAPOX treatment. The PFS HR was 0.687 (95% CI: 0.544, 0.866; 1-sided P = 0.0007) and the OS HR was 0.771 (95% CI: 0.615, 0.965; 1-sided P = 0.0118).

The updated PFS and final OS analysis for GLOW are presented in table 5 and Figures 3-4 show the Kaplan- Meier curves.

Table 5. Efficacy results in SPOTLIGHT and GLOW

Endpoint	SPOTLIGHT[a]		GLOW[b]	
	Zolbetuximab with mFOLFOX6 n=283	**Placebo with mFOLFOX6 n=282**	**Zolbetuximab with CAPOX n=254**	**Placebo with CAPOX n=253**
Progression-free survival				
Number (%) of patients with events	159 (56.2)	187 (66.3)	153 (60.2)	182 (71.9)
Median in months (95% CI)[c]	11.0 (9.7, 12.5)	8.9 (8.2, 10.4)	8.2 (7.3, 8.8)	6.8 (6.1, 8.1)
Hazard ratio (95% CI)[d,e]	0.734 (0.591, 0.910)		0.689 (0.552, 0.860)	
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)	
Objective response rate (ORR), Duration of response (DOR)				
ORR (%) (95% CI)[f]	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)[f]	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. SPOTLIGHT data cut-off: 08-Sep-2023, median follow-up time of zolbetuximab in combination with mFOLFOX6 arm was 18.0 months.
b. GLOW data cut-off: 12-Jan-2024, median follow-up time of zolbetuximab in combination with CAPOX arm 20.6 months.
c. Based on Kaplan-Meier estimate.
d. Stratification factors were region, number of metastatic sites, prior gastrectomy from interactive response technology and study ID (SPOTLIGHT/GLOW).
e. Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites, prior gastrectomy as the explanatory variables and study ID (SPOTLIGHT/GLOW).
f. Based on IRC assessment and unconfirmed responses.

A combined efficacy analysis of SPOTLIGHT and GLOW of the final OS and updated PFS resulted in a median PFS (as assessed by IRC) of 9.2 months (95% CI: 8.4, 10.4) for zolbetuximab in combination with mFOLFOX6/CAPOX versus 8.2 months (95% CI: 7.6, 8.4) for placebo with mFOLFOX6/CAPOX [HR 0.712, 95% CI: 0.610, 0.831] and a median OS for zolbetuximab in combination with mFOLFOX6/CAPOX of 16.4 months (95% CI: 15.0, 17.9) versus 13.7 months (95% CI: 12.3, 15.3) for placebo with mFOLFOX6/CAPOX [HR 0.774, 95% CI: 0.672, 0.892].

Figure 1. Kaplan Meier plot of progression-free survival, SPOTLIGHT

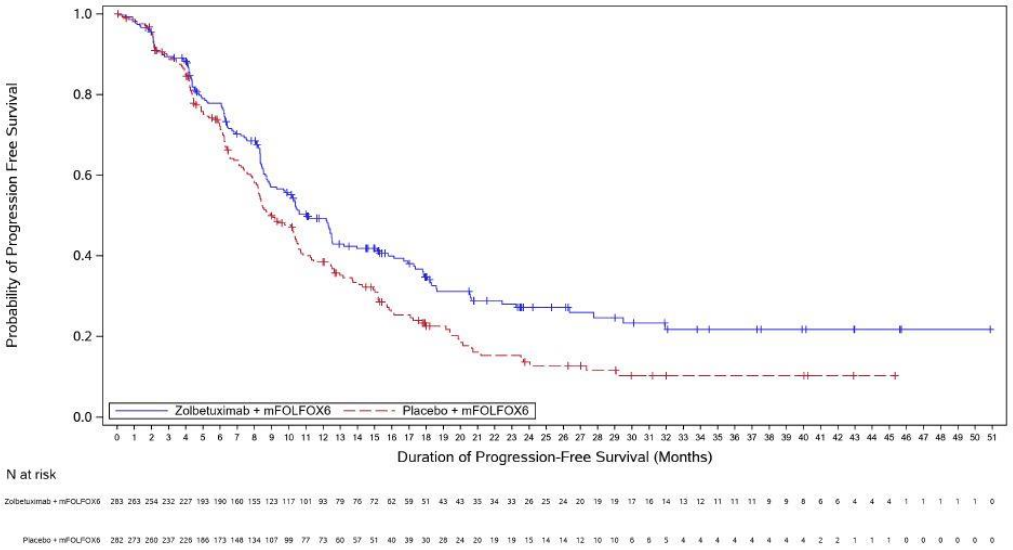


Figure 2. Kaplan Meier plot of overall survival, SPOTLIGHT

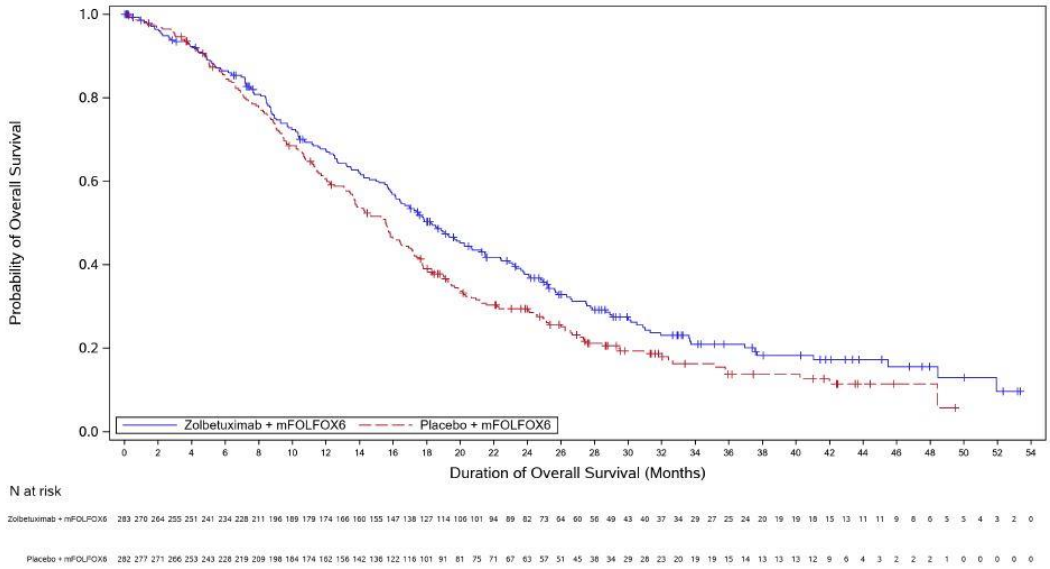


Figure 3. Kaplan Meier plot of progression-free survival, GLOW

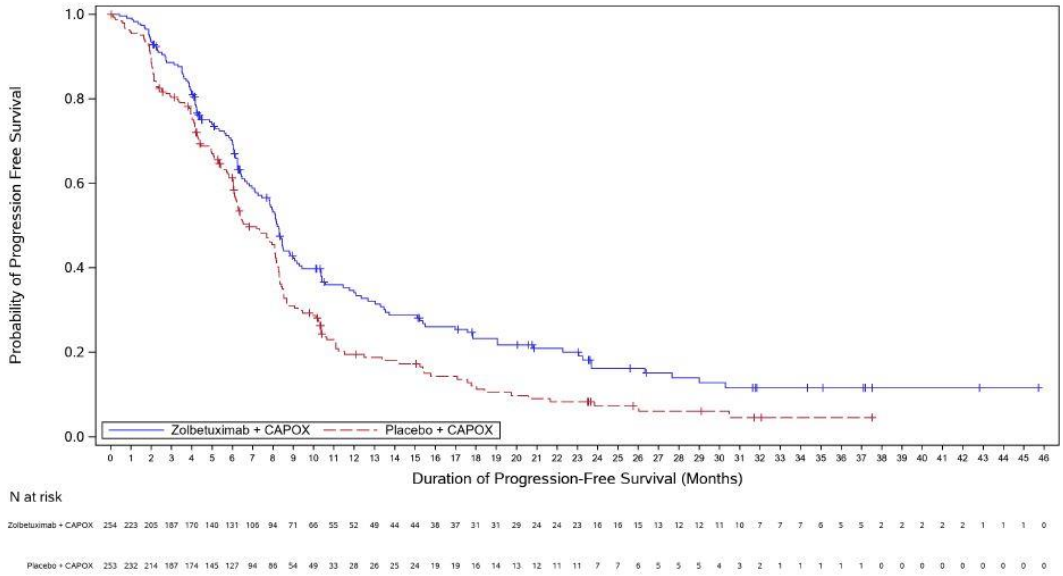
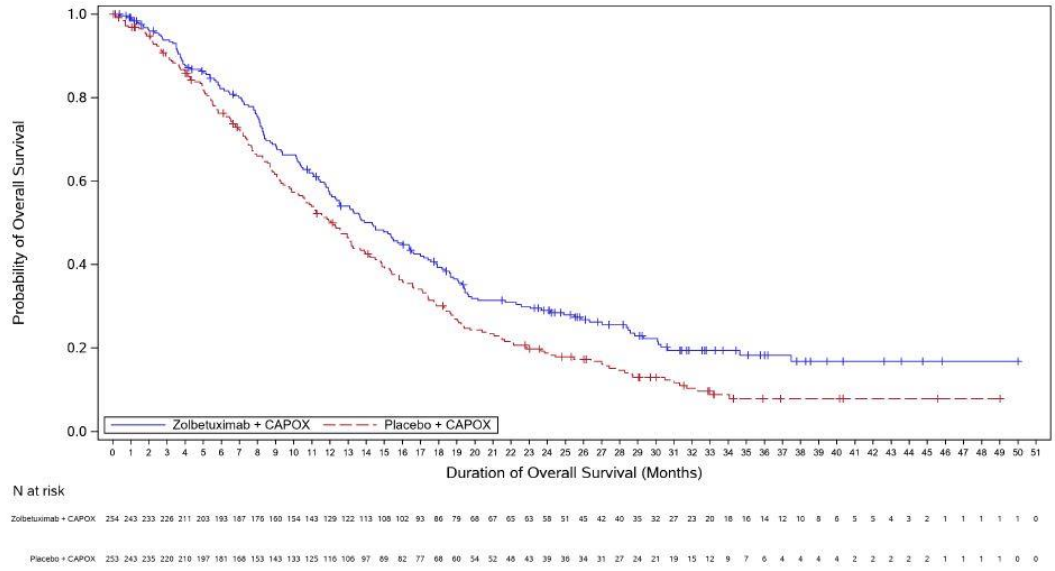


Figure 4. Kaplan Meier plot of overall survival, GLOW



Exploratory subgroup analyses of efficacy for SPOTLIGHT and GLOW showed a difference in PFS and OS for Caucasian versus Asian patients.

For SPOTLIGHT, in Caucasian patients this resulted in a PFS (as assessed by IRC) with a HR of 0.872 [95% CI: 0.653, 1.164] and an OS HR of 0.940 [95% CI: 0.718, 1.231] for zolbetuximab in combination with mFOLFOX6 versus placebo with mFOLFOX6. In Asian patients, this resulted in a PFS (as assessed by IRC) with a HR of 0.526 [95% CI: 0.354, 0.781] and an OS HR of 0.636 [95% CI: 0.450, 0.899] for zolbetuximab in combination with mFOLFOX6 versus placebo with mFOLFOX6. For GLOW, in Caucasian patients this resulted in a PFS (as assessed by IRC) with a HR of 0.891 [95% CI: 0.622, 1.276] and an OS HR of 0.805 [95% CI: 0.579, 1.120] for zolbetuximab in combination with CAPOX versus placebo with CAPOX. In Asian patients, this resulted in a PFS (as assessed by IRC) with a HR of 0.616 [95% CI: 0.467, 0.813] and an OS HR of 0.710 [95% CI: 0.549, 0.917] for zolbetuximab in combination with CAPOX versus placebo with CAPOX.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with zolbetuximab in all subsets of the paediatric population in gastric or GEJ adenocarcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following intravenous administration, zolbetuximab 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 24 weeks with a mean (SD) C_{max} and AUC_{tau} at 453 (82) µg/mL and 4125 (1169) day•µg/mL, respectively, based on a population pharmacokinetic analysis. When administered at 800/400 mg/m^2 every 2 weeks, steady state is expected to be achieved by 22 weeks with a mean (SD) C_{max} and AUC_{tau} at 359 (68) µg/mL and 2758 (779) day•µg/mL, respectively, based on a population pharmacokinetics analysis.

Distribution

The estimated mean steady state volume of distribution of zolbetuximab was 5.5 L.

Biotransformation

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

Elimination

Zolbetuximab clearance (CL) decreased over time, with a maximal reduction from baseline values of 57.6% resulting in a population mean steady-state clearance (CL_{ss}) of 0.0117 L/h. The half-life of zolbetuximab ranged from 7.6 to 15.2 days during treatment.

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 zolbetuximab.

Race and gender

Based on the population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified based on gender [62.3% male, 37.7% female] or race [50.1% Caucasian, 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 GEJ adenocarcinoma, no clinically significant differences in the pharmacokinetics of zolbetuximab 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 Cockcroft-Gault formula. Zolbetuximab has only been evaluated in a limited number of patients with severe renal impairment (CrCL ≥15 to <30 mL/min; n=1). The effect of severe renal impairment on the pharmacokinetics of zolbetuximab is unknown.

Hepatic impairment

Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GEJ adenocarcinoma, no clinically significant differences in the pharmacokinetics of

zolbetuximab were identified in patients with mild hepatic impairment as measured by TB and AST (TB ≤ ULN and AST > ULN, or TB > 1 to 1.5 × ULN and any AST; n=108). Zolbetuximab has only been evaluated in a limited number of patients with moderate hepatic impairment (TB > 1.5 to 3 × ULN and any AST; n=4) and has not been evaluated in patients with severe hepatic impairment (TB > 3 to 10 × ULN and any AST). The effect of moderate or severe hepatic impairment on the pharmacokinetics of zolbetuximab is unknown.

5.3 Preclinical safety data

No studies in animals have been performed to evaluate carcinogenicity or mutagenicity.

No toxicity or other zolbetuximab-related adverse effects on the cardiovascular, respiratory or central nervous systems was observed in mice administered zolbetuximab for 13 weeks at systemic exposures up to 7.0-fold the human exposure at the recommended dose of 600 mg/m^2 (based on AUC) or in cynomolgus monkeys administered zolbetuximab for 4 weeks at systemic exposures up to 6.1-fold the human exposure at the recommended dose of 600 mg/m^2 (based on AUC).

In an embryo-foetal development toxicity study, where zolbetuximab was administered to pregnant mice during the period of organogenesis at systemic exposures up to approximately 6.2-fold the human exposure at the recommended dose of 600 mg/m^2 (based on AUC), zolbetuximab crossed the placental barrier. The resulting concentration of zolbetuximab in foetal serum at Day 18 of gestation was higher than that in the maternal serum at Day 16 of gestation. Zolbetuximab did not result in any external or visceral foetal abnormalities (malformations or variations).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine
Phosphoric acid (E 338)
Sucrose
Polysorbate 80 (E 433)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

4 years.

Reconstituted solution in the vial

Reconstituted vials may be stored at room temperature (≤ 25 °C) for up to 6 hours. Do not freeze them nor expose them to direct sunlight. Discard unused vials with reconstituted solution beyond the recommended storage time.

Diluted solution in the infusion bag

From a microbiological point of view, the diluted solution in the bag should be administered immediately. If not administered immediately, the prepared infusion bag should be stored:

- under refrigeration (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 (≤ 25 °C) for no longer than 8 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 in a refrigerator (2 ºC – 8 ºC).
Do not freeze.
Store in the original package 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

Vyloy 100 mg powder for concentrate for solution for infusion vial
20 mL Type I glass vial with European blow-back feature, grey bromobutyl rubber stopper with ethylene tetrafluoroethylene film, and aluminum seal with a green cap.

Vyloy 300 mg powder for concentrate for solution for infusion vial
50 mL Type I glass vial with European blow-back feature, grey bromobutyl rubber stopper with ethylene tetrafluoroethylene film, and aluminum seal with a violet cap.

Pack sizes 100 mg: one carton containing 1 or 3 vials.
Pack size 300 mg: one carton containing 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for preparation and administration

Reconstitution in single-dose vial
- Follow procedures for proper handling and disposal of anticancer medicinal products.
- Use appropriate aseptic technique for reconstitution and preparation of solutions.
- Calculate the recommended dose based on the patient's body surface area to determine the number of vials needed.
- Reconstitute each vial as follows. If possible, direct the stream of sterile water for injections (SWFI) along the walls of the vial and not directly onto the lyophilised powder:
  a. 100 mg vial: Slowly add 5 mL of SWFI, resulting in 20 mg/mL zolbetuximab.
  b. 300 mg vial: Slowly add 15 mL of SWFI, resulting in 20 mg/mL zolbetuximab.
- 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.
- Visually inspect the solution for particulate matter and discolouration. 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 discolouration.
- 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 for storage of reconstituted vials.

Dilution in infusion bag
- Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
- Dilute with sodium chloride 9 mg/mL (0.9%) solution for infusion. The infusion bag size should allow enough diluent to achieve a final concentration of 2 mg/mL zolbetuximab.

The diluted dosing solution of zolbetuximab is compatible with intravenous infusion bags composed of polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with either plasticizer [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, polyurethane (PU), PVC with either plasticizer [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.

- Mix the diluted solution by gentle inversion. Do not shake the bag.
- 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.
- Discard any unused portion left in the single-dose vials.

Administration
- Do not co-administer other medicinal products through the same infusion line.
- Administer the infusion immediately over a minimum of 2 hours through an intravenous line. Do not administer as an intravenous 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 plasticizer [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 plasticizer [TOTM].

- In-line filters (pore size of 0.2 μm with materials listed above) are recommended to be used during administration.
- If not administered immediately, refer to section 6.3 for storage of the prepared infusion bag.

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

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

EU/1/24/1856/001
EU/1/24/1856/002
EU/1/24/1856/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

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

Name and address of the manufacturer of the biological active substance

Patheon Biologics LLC
4766 LaGuardia Drive,
Saint Louis, Missouri (MO) 63134-3116
United States

Name and address of the manufacturer responsible for batch release

Astellas Ireland Co. Limited
Killorglin Co. Kerry
V93 FC86
Ireland

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vyloy 100 mg powder for concentrate for solution for infusion.
zolbetuximab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of powder contains 100 mg zolbetuximab.
After reconstitution, each mL of solution contains 20 mg of zolbetuximab.

3. LIST OF EXCIPIENTS

Contains arginine, phosphoric acid (E 338), sucrose, and polysorbate 80 (E 433).

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial
3 vials

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.
Do not shake.
For single use only.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package 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

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1856/001
EU/1/24/1856/002

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

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Vyloy 100 mg powder for concentrate for solution for infusion.
zolbetuximab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 100 mg zolbetuximab.
After reconstitution, each mL contains 20 mg of zolbetuximab.

3. LIST OF EXCIPIENTS

Contains arginine, E 338, sucrose, and E 433.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For IV use after reconstitution and dilution.
Do not shake.
For single use only.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package 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

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1856/001
EU/1/24/1856/002

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

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vyloy 300 mg powder for concentrate for solution for infusion.
zolbetuximab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of powder contains 300 mg zolbetuximab.
After reconstitution, each mL of solution contains 20 mg of zolbetuximab.

3. LIST OF EXCIPIENTS

Contains arginine, phosphoric acid (E 338), sucrose, and polysorbate 80 (E 433).

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.
Do not shake.
For single use only.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package 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

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2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1856/003

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

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Vyloy 300 mg powder for concentrate for solution for infusion.
zolbetuximab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 300 mg zolbetuximab.
After reconstitution, each mL contains 20 mg of zolbetuximab.

3. LIST OF EXCIPIENTS

Contains arginine, E 338, sucrose, and E 433.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For IV use after reconstitution and dilution.
Do not shake.
For single use only.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package 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

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1856/003

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

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vyloy 100 mg powder for concentrate for solution for infusion
Vyloy 300 mg powder for concentrate for solution for infusion
zolbetuximab

▼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.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Vyloy is and what it is used for

Vyloy contains the active substance zolbetuximab, which is a monoclonal antibody that can recognise and attach to certain cancer cells. By attaching to these cancer cells, the medicine causes the immune system to attack and kill them.

This medicine is used to treat adults with stomach (gastric) or gastro-oesophageal junction cancer. The gastro-oesophageal junction is the place where the oesophagus (gullet) joins the stomach.

This medicine is given to patients whose tumours are positive for the *Claudin18.2 (CLDN18.2)* protein (meaning the protein is produced in the cells), and negative for the "Human epidermal growth factor receptor 2 (HER2)" proteins (meaning that no or only small amounts of the protein are produced). It is given to patients whose gastric or gastro-oesophageal junction cancer cannot be removed by surgery or has spread to other parts of the body.

This medicine is given in combination with other anti-cancer medicines that contain fluoropyrimidine and/or platinum. It is important that you also read the package leaflets for these other medicines. If you have any questions about these medicines, ask your doctor.

2. What you need to know before you are given Vyloy

You must not be given Vyloy
- if you are allergic to zolbetuximab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before you are given this medicine as it may cause:
- **Allergic (hypersensitivity) reactions**, **including anaphylaxis.** Serious allergic reactions can happen during or after you receive your infusion. Tell your doctor or get medical help right away if you have any of the following symptoms of a serious allergic reaction:
  - itchy, swollen pink or red areas of the skin (hives),
  - coughing that doesn't go away,
  - breathing problems such as wheezing, or
  - throat tightness/change in voice
- **Infusion-related reactions.** Severe reactions linked to the infusion (drip) can happen during or after you receive your infusion. Tell your doctor or get medical help right away if you have any of the following symptoms of an infusion related reaction:
  - nausea (feeling sick),
  - vomiting (being sick),
  - stomach pain,
  - increased saliva (salivary hypersecretion),
  - fever,
  - chest discomfort,
  - chills or shaking,
  - back pain,
  - cough, or
  - high blood pressure (hypertension)
- **Nausea and vomiting.** Tell your doctor if you are feeling sick before the infusion starts. Nausea and vomiting are very common during treatment and can sometimes be severe. Your doctor may give you another medicine before each infusion to help relieve nausea and vomiting.

Tell your doctor immediately if you have any of these signs or symptoms or if they get worse. Your doctor may:
- give you other medicines in order to reduce your symptoms or prevent complications,
- decrease the speed of the infusion, or
- stop your treatment for a period of time or completely.

Children and adolescents
There is no relevant use of Vyloy in children and adolescents, because it has not been studied in this age group for the treatment of stomach (gastric) or gastro-oesophageal junction cancer.

Other medicines and Vyloy
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy
Vyloy should not be used if you are pregnant unless your doctor specifically recommends it. It is not known if this medicine will harm your unborn baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Breast-feeding
Breast-feeding is not recommended during treatment with Vyloy. It is not known if this medicine passes into your breast milk. Tell your doctor if you are breast-feeding or plan to breast-feed.

Driving and using machines
Vyloy is unlikely to affect your ability to drive or use machines.

Vyloy contains polysorbate 80
This medicine contains 1.05 mg and 3.15 mg of polysorbate 80 in each 100 mg and 300 mg dose of Vyloy, respectively. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Vyloy infusion contains sodium
This medicine does not contain sodium, however, a salt solution is used for the dilution of this product prior to infusion. Talk to your doctor if you are on a low salt diet.

3. How Vyloy is given

You will receive Vyloy in a hospital or clinic under the supervision of a doctor experienced in cancer treatment. This medicine will be given to you as an intravenous infusion (drip) into your vein over a period of at least 2 hours.

How much Vyloy you will receive
Your doctor will decide how much of this medicine you will receive. You will usually receive this medicine every 2 or 3 weeks based on the other anti-cancer medicines chosen by your doctor. Your doctor will decide how many treatments you need.

If you miss a dose of Vyloy
It is very important that you do not miss a dose of this medicine. If you miss an appointment, call your doctor to reschedule your appointment as soon as possible.

If you stop treatment with Vyloy
Do not stop treatment with this medicine unless you have discussed this with your doctor. Stopping your treatment may stop the effect of the medicine.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some possible side effects may be serious:

- **Hypersensitivity (allergic) reactions (including hypersensitivity and anaphylactic reaction) – common** (may affect up to 1 in 10 people). Tell your doctor or get medical help right away if you have any of these symptoms of a serious allergic reaction: itchy, swollen pink or red areas of the skin (hives), coughing that doesn't go away, breathing problems such as wheezing, or throat tightness/change in voice.

- **Infusion related reaction – common** (may affect up to 1 in 10 people). Tell your doctor or get medical help right away if you have any of these symptoms of an infusion related reaction: nausea, vomiting, stomach pain, increased saliva (salivary hypersecretion), fever, chest discomfort, chills or shaking, back pain, cough, or high blood pressure (hypertension).

- **Nausea and vomiting – very common** (may affect more than 1 in 10 people). Tell your doctor if these symptoms do not go away or become worse.

Other possible side effects:

If these side effects become severe, tell your doctor.

Very common (may affect more than 1 in 10 people):
- decreased appetite
- low white blood cell count
- low levels of albumin in the blood (hypoalbuminaemia)
- swelling of the lower legs or hands (peripheral oedema)
- decreased weight
- fever (pyrexia)

Common (may affect up to 1 in 10 people):
- indigestion (dyspepsia)
- increased saliva (salivary hypersecretion)
- increased blood pressure (hypertension)
- chills

Reporting of side effects
If you get any side effects, talk to your doctor. 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 Vyloy

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 vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 ºC – 8 ºC). Do not freeze. Store in the original package in order to protect from light.

Do not store any unused portion of the single-dose vials for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Vyloy contains
- The active substance is zolbetuximab.
- One vial of 100 mg powder for concentrate for solution for infusion contains 100 mg zolbetuximab.
- One vial of 300 mg powder for concentrate for solution for infusion contains 300 mg zolbetuximab.
- After reconstitution, each ml of solution contains 20 mg of zolbetuximab.
- The other ingredients are arginine, phosphoric acid (E 338), sucrose, and polysorbate 80 (E 433) (see section 2 “Vyloy contains polysorbate 80”).

What Vyloy looks like and contents of the pack
Vyloy powder for concentrate for solution for infusion is a white to off-white lyophilised powder.

Vyloy is supplied in a carton containing 1 or 3 glass vials.

Not all pack sizes may be marketed.

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Manufacturer
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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

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.

Instructions for preparation and administration

Reconstitution in single-dose vial

- Follow procedures for proper handling and disposal of anticancer medicinal products.
- Use appropriate aseptic technique for reconstitution and preparation of solutions.
- Calculate the recommended dose based on the patient's body surface area to determine the number of vials needed.
- Reconstitute each vial as follows. If possible, direct the stream of sterile water for injections (SWFI) along the walls of the vial and not directly onto the lyophilised powder:

a. 100 mg vial: Slowly add 5 mL of SWFI, resulting in 20 mg/mL zolbetuximab.
b. 300 mg vial: Slowly add 15 mL of SWFI, resulting in 20 mg/mL zolbetuximab.

- 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(s).
- Visually inspect the solution for particulate matter and discolouration. 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 discolouration.
- 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.

Dilution in infusion bag

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

The diluted dosing solution of zolbetuximab is compatible with intravenous infusion bags composed of polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with either plasticizer [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, polyurethane (PU), PVC with either plasticizer [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.

- Mix the diluted solution by gentle inversion. Do not shake the bag.
- 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.
- Discard any unused portion left in the single-dose vials.

Administration

- Do not co-administer other medicinal products through the same infusion line.
- Administer the infusion immediately over a minimum of 2 hours through an intravenous line. Do not administer as an intravenous 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 plasticizer [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 plasticizer [TOTM].

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

Disposal

Vyloy is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.