swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vyloy

International non-proprietary name:	zolbetuximab
Pharmaceutical form:	powder for concentrate for solution for infusion
Dosage strength(s):	100 mg
Route(s) of administration:	intravenous
Marketing authorisation holder:	Astellas Pharma AG
Marketing authorisation no.:	69501
Decision and decision date:	approved on 19 February 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CLDN18.2	Claudin 18 isoform 2
C_{max}	Maximum observed plasma/serum concentration of drug
DOR	Duration of response
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
HER2	Human epidermal growth factor receptor 2
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
WCB	Working cell bank
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for zolbetuximab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 19 October 2023.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia and Singapore.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are CLDN18.2 positive.

2.2.2 Approved indication

VYLOY, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative, claudin (CLDN) 18.2-positive gastric adenocarcinoma (see "*Clinical Efficacy*").

2.2.3 Requested dosage

Summary of the requested standard dosage:
Vyloy is given as an intravenous infusion with an increasing infusion rate.
Treatment starts with a single loading dose of 800 mg/m^2 body surface area on day 1 of cycle 1, followed by maintenance doses of 600 mg/m^2 every third week (Q3W) or 400 mg/m^2 every second week (Q2W).
The length of the cycles is determined by the chosen chemotherapy regimen.
Treatment is maintained until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	24 November 2023
Formal objection	28 November 2023
Response to formal objection	7 December 2023
Formal control completed	22 December 2023
List of Questions (LoQ)	19 April 2024
Response to LoQ	19 June 2024
2nd List of Questions (LoQ)	30 July 2024
Response to 2nd LoQ	18 August 2024
Preliminary decision	10 September 2024
Response to preliminary decision	6 November 2024
Labelling corrections and/or other aspects	23 December 2024
Response to labelling corrections and/or other aspects	19 January 2025
2nd round labelling corrections and/or other aspects	7 February 2025
Response to 2nd round labelling corrections and/or other aspects	12 February 2025
Final decision	19 February 2025
Decision	approval

3 Quality aspects

3.1 Drug substance

Zolbetuximab 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. Zolbetuximab binds to claudin 18 isoform 2 (CLDN18.2) on the surface of target cells, followed by antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), which are both mediated by the monoclonal antibody Fc region. Zolbetuximab is a glycoprotein (molecular weight approx. 147 kDa) composed of two heavy chains and two light chains covalently linked with nine interchain disulphide bonds.
Zolbetuximab is produced in Chinese hamster ovary (CHO) cells. A two-tiered cell banking system of Master Cell Bank and Working Cell Bank (WCB) is in place. After thawing of the WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The cell culture fluid is harvested, and purification is performed with a series of chromatography steps, ultrafiltration/diafiltration steps as well as viral inactivation and viral filtration steps.

The cell culture and purification processes for zolbetuximab drug substance are both validated with several consecutive batches and the data demonstrated a consistent production and efficient removal of impurities. The physicochemical and biological properties of the zolbetuximab drug substance and its impurities were characterised using state-of-the-art methods.

Several changes were implemented during development of the manufacturing process for the drug substance, including changes to manufacturing site and production scale. However, comparability studies, including batch release data, extended characterisation data, and forced degradation stability data, demonstrated comparability between the different processes.
The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on published limits, stability data, clinical experience and batch analysis data as well as stability data. Specifications are in conformance with current compendial or regulatory guidelines. Batch analysis data for development, clinical, and process validation batches of zolbetuximab drug substance were provided. All specific analytical methods are described and are fully validated.

No significant changes were observed during storage of zolbetuximab drug substance under the proposed storage conditions.

3.2 Drug product

Zolbetuximab drug product is a sterile, preservative-free, white to off-white lyophilised powder, supplied in a single-dose vial. The dose strength of zolbetuximab drug product is 100 mg/vial. Prior to administration, the zolbetuximab drug product is reconstituted with 5.0 mL of sterile water for injection. The composition of reconstituted zolbetuximab drug product is 20 mg/mL zolbetuximab, arginine, sucrose, and polysorbate 80, q.s. to pH 6.0 phosphoric acid. The reconstituted solution is subsequently diluted in sterile 0.9% w/v sodium chloride injection in an intravenous infusion bag prior to administration.
All excipients used in the zolbetuximab drug product (arginine, phosphoric acid, polysorbate 80, sucrose and water for injection) are tested in accordance with current compendial methods to the corresponding compendial specification. In addition, there are no novel excipients or excipients of human or animal origin in the zolbetuximab drug product.
Several drug product dosage strengths and filling facilities were used during clinical development. However, comparability studies, which included batch release data, extended characterisation data, and forced degradation data, demonstrated comparability of the relevant quality attributes between

the different processes. Compatibility studies were conducted to establish the in-use stability of the diluted drug product with the intended materials and conditions of use.

The drug product manufacturing process consists of drug substance thawing, compounding, sterile filtration, aseptic filling, lyophilisation and capping followed by visual inspection, labelling, and secondary packaging. The drug product manufacturing process is validated with several consecutive batches. The data demonstrated a consistent production.

The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug product, including development batches, clinical batches, and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are validated.
The container closure system consists of a 20 mL clear Type I glass vial with European blow-back feature, a 20 mm gray bromobutyl rubber stopper and an aluminium seal with flip-off top. The materials of the type I glass vial and rubber stopper meet compendial requirements.

The vials are stored at 2°C to 8°C. The stability data support a shelf life of 48 months.

3.3 Quality conclusions

Satisfactory and consistent quality of the Drug Substance and Drug Product has been demonstrated. Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority (Australia's Therapeutic Goods Administration (TGA), see section 2.1 Applicant's request / Work-sharing procedure).

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority (Singapore's Health Sciences Authority (HSA), see section 2.1 Applicant's request / Work-sharing procedure).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Vyloy was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "*Undesirable effects*" section for advice on the reporting of adverse reactions.

VYLOY™

Composition

Active substances

Zolbetuximab (manufactured from genetically modified CHO [Chinese Hamster Ovary] cells).

Excipients

Arginine, phosphoric acid (E338), sucrose and polysorbate 80 (E433).

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion. White to off-white lyophilised powder. Each vial contains an extractable amount of 100 mg of zolbetuximab after reconstitution, for a final concentration of 20 mg/mL.

Indications/Uses

VYLOY, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative, claudin (CLDN) 18.2-positive gastric adenocarcinoma (see "*Clinical Efficacy*").

Dosage/Administration

Treatment with VYLOY should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Patient Selection
Select patients with locally advanced unresectable or metastatic HER2-negative gastric 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 "*Clinical Efficacy*").

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 "*Warnings and Precautions*").

Recommended Dose

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 "*Properties/Effects*").	600 mg/m^2 intravenously every 3 weeks or 400 mg/m^2 intravenously every 2 weeks Administer VYLOY in combination with fluoropyrimidine- and platinum-containing chemotherapy (see "*Properties/Effects*").	Until disease progression or unacceptable toxicity.

a. The cycle duration of VYLOY is determined based on the respective chemotherapy backbone (see "*Clinical Efficacy*").

Refer to the fluoropyrimidine- or platinum-containing chemotherapy prescribing information regarding the dosing information for combined chemotherapy.

The dosing regimen of 400 mg/m² every 2 weeks for the maintenance dose has not been studied in clinical trials. This dosing regimen is based on modeling and simulation analyses, and there are no clinical data available (See "*Pharmacokinetics*").

Dose Modifications

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

Table 2. Dose Modifications for VYLOY

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

Patients with impaired hepatic function

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). Zolbetuximab has only been evaluated in a limited number of patients with moderate hepatic impairment and has not been evaluated in patients with severe hepatic impairment (see "*Pharmacokinetics*").

Patients with impaired renal function

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. Zolbetuximab has only been evaluated in a limited number of patients with severe renal impairment (CrCL ≥15 to <30 mL/min) (see "*Pharmacokinetics*").

Elderly patients

No dose adjustment is required in patients ≥65 years of age. Of the 533 patients in clinical studies of VYLOY in combination with mFOLFOX6 or CAPOX, 34% (n=179) were over 65 years, and 5% were over 75 years (n=28).

Children and adolescents

Zolbetuximab is not authorised for treatment in the pediatric population.

Mode of administration

VYLOY is for intravenous use. The recommended dose is administered by intravenous infusion according to the infusion rates presented in Table 3. 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 "*Shelf-life after dilution/reconstitution*" 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 "*Clinical Efficacy*").

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 "*Instructions for handling*".

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

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 "*Undesirable Effects*").

Patients should be monitored 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).

If an anaphylactic reaction occurs, administration of VYLOY should be immediately and permanently discontinued and appropriate medical therapy administered.

For any Grade 3 or 4 hypersensitivity reaction or hypersensitivity reaction with features of anaphylaxis, administration of VYLOY should be immediately and permanently discontinued and appropriate medical therapy instituted based on the type of reaction.

For any Grade 2 hypersensitivity reaction, interrupt the VYLOY infusion until Grade ≤1, then resume the infusion at a reduced infusion rate for the remaining infusion. Pre-medicate the patient

with antihistamines for the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of a hypersensitivity reaction. The infusion rate may be gradually increased as tolerated (see "*Dosage/Administration*").

Infusion-related reactions

Infusion-related reactions (IRR) have occurred during clinical studies with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy (see "*Undesirable Effects*").
Monitor patients 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.
For Grade 3 or 4 IRRs, administration of VYLOY should be immediately and permanently discontinued and appropriate medical therapy instituted.
For Grade 2 IRRs, interrupt the VYLOY infusion until Grade ≤1, then resume the infusion at a reduced infusion rate for the remaining infusion. Pre-medicate the patient with antihistamines for the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of an IRR. The infusion rate may be gradually increased as tolerated (see "*Dosage/Administration*").

Gastrointestinal Haemorrhage

Gastrointestinal (GI) haemorrhage has been observed in patients receiving VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy. Monitor patients for signs and symptoms of GI haemorrhage during treatment. Promptly evaluate and treat any suspected GI haemorrhage.

Nausea and Vomiting

During clinical studies, nausea and vomiting were the most frequently observed GI adverse reactions with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy treatment (see "*Undesirable 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.
Nausea and vomiting occurred more often during the first cycle of treatment but decreased in incidence with subsequent cycles of treatment.
To prevent nausea and vomiting, pretreatment with a combination of antiemetics is recommended prior to each infusion of VYLOY (see "*Dosage/Administration*").
During and after infusion, patients should be monitored and managed using standard of care, including antiemetics or fluid replacement, as clinically indicated.
For Grade 4 vomiting, permanently discontinue treatment with VYLOY.

For Grade 2 or 3 nausea or vomiting, interrupt the VYLOY infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. For the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of nausea or vomiting. The infusion rate may be gradually increased as tolerated (see "*Dosage/Administration*").

Posterior Reversible Encephalopathy Syndrome (PRES)

Among patients treated with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy, the occurrence of PRES has been observed, 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.

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 studies or transporter studies have been conducted.

Effect of zolbetuximab on other medicinal products

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

Effect of other medicinal products on zolbetuximab

Coadministration with mFOLFOX6 did not impact zolbetuximab pharmacokinetics. No dose adjustment is required for zolbetuximab when used in combination with fluoropyrmidine- and platinum-containing chemotherapy.

Pregnancy, lactation

Pregnancy

There are no data on the use of zolbetuximab in pregnant women. Studies in animals revealed no reproductive toxicity. VYLOY should only be given to a pregnant woman if the benefit outweighs the potential risk.

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. Because many antibodies are excreted in human milk and because of the potential for serious adverse reactions in a breastfed child, breastfeeding is not recommended during treatment with VYLOY.

Fertility

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

Effects on ability to drive and use machines

Nausea has been reported in patients taking VYLOY and should be considered when assessing a patient's ability to drive or use machines. No corresponding studies have been performed.

Undesirable effects

The safety of VYLOY was evaluated in the integrated safety population from two phase 2 studies and two phase 3 studies (SPOTLIGHT, GLOW) in 631 patients who received at least one dose of VYLOY 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 VYLOY in combination with 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 VYLOY in combination with 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 VYLOY in combination with fluoropyrimidine and 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 VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy infusion were nausea (9.7%) and vomiting (7.8%).

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

VYLOY with fluoropyrimidine and platinum-containing chemotherapy	
Blood and lymphatic system disorders	
Very common	Neutropenia (30.7%), Neutrophil count decreased (28.4%)
Immune system disorders	
Common	Drug hypersensitivity
Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	
Very common	Hypoalbuminemia (17.1%), decreased appetite (42.0%)
Vascular disorders	
Common	Hypertension
Gastrointestinal disorders	
Very common	Vomiting (66.9%), nausea (77.2%)
Common	Salivary hypersecretion, dyspepsia
General disorders and administration site conditions	
Very common	Edema peripheral (13.9%), pyrexia (17.4%)
Common	Chills
Investigations	
Very common	Weight decreased (21.9%)
Injury, poisoning and procedural complications	
Common	Infusion related reaction
Nervous system disorders	
Uncommon	Posterior Reversible Encephalopathy Syndrome

Description of specific adverse reactions

Hypersensitivity reactions

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

Severe (Grade 3) anaphylactic reaction or drug hypersensitivity occurred with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 0.5% (3/631) and 0.2% (1/631). The median time to onset of anaphylactic reaction or drug hypersensitivity with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy was 22 days or 113 days, respectively.

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

Infusion related reaction

In the integrated safety analysis, all grade IRR occurred with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 3.2% (20/631).
Severe (Grade 3) IRR occurred in 0.5% (3/631) of patients treated with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy. The median time to onset of infusion-related reaction with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy was 22 days.
An IRR led to permanent discontinuation of VYLOY in combination with 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 in combination with 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 with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 77.2% (487/631) and 66.9% (422/631), respectively.
Severe (Grade 3) nausea or vomiting occurred with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 11.6% (73/631) and 13.6% (86/631). The median time to onset of nausea or vomiting with VYLOY in combination with fluoropyrimidine and platinum-containing chemotherapy was 1 day for each.
Nausea led to permanent discontinuation of VYLOY in combination with 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 in combination with 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 in combination with fluoropyrimidine and platinum-containing chemotherapy in 61 patients (9.7%) due to nausea and in 49 patients (7.8%) due to vomiting.

Cardiac electrophysiology

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

Immunogenicity

In an approximately 30-month treatment period of 2 clinical studies of VYLOY 800/600 mg/m^2 every 3 weeks in combination with mFOLFOX6/CAPOX in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive, 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 ADAs, the effect of these antibodies on the pharmacokinetics, safety and/or effectiveness of zolbetuximab is unknown.

The incidence of anti-drug-antibodies (ADA) depends largely on sensitivity and specificity of the test. Further the observed incidence of antibody positivity (including neutralising antibodies) in a test can be influenced by several factors, for example test methodology, sample handling, timepoint of sampling, co-medication and underlying illness. Therefore, the comparison of the incidence of antibodies against zolbetuximab with the incidence of antibodies against other drugs can be misleading.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code:
L01FX31

Mechanism of action

Zolbetuximab is a genetically engineered, 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 mouse 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.

Pharmacodynamics

See "*Pharmacokinetics*" regarding statements on the C_{max} and C_{min} values resulting from the dosing regimens.

Clinical efficacy

SPOTLIGHT (8951-CL-0301)

The safety and efficacy of VYLOY in combination with mFOLFOX6 was evaluated in a phase 3, double-blind, randomised, multicentre study that enrolled 565 patients whose tumours were CLDN18.2 positive, HER2-negative, with locally advanced unresectable or metastatic gastric (n = 429) or gastroesophageal junction (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 VYLOY in combination with mFOLFOX6 (n=283) or placebo in combination with mFOLFOX6 (n=282). VYLOY 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 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.

Patients were excluded from the study 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.

Treatment with VYLOY continued until RECIST v1.1-defined progression of disease as determined by an independent review committee (IRC), unacceptable toxicity or a subsequent anticancer treatment was initiated. Tumour assessments were performed every 9 weeks up to and including week 54, then every 12 weeks thereafter.

The primary efficacy outcome was Progression Free Survival (PFS) as assessed per RECIST v1.1 by 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.

Among patients who received VYLOY or placebo in combination with mFOLFOX6, the median age of patients included was 61 years (range: 20 to 86); 62% were male; 53% were White, 38% were Asian. 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).

In patients with gastric adenocarcinoma, the median PFS (determined by an IRC, data cut-off September 2022) for VYLOY in combination with mFOLFOX6 was 12.2 months (95% CI: 9.3; 14.0) compared to 8.4 months (95% CI: 7.8; 10.3) for placebo in combination with mFOLFOX6 (HR = 0.694; 95% CI: 0.534; 0.902).

In patients with gastric adenocarcinoma, the median OS (data cut-off September 2022) for VYLOY in combination with mFOLFOX6 was 20.2 months (95% CI:17.0, 24.1) compared to 13.8 months (95% CI: 11.9, 16.5) for placebo in combination with mFOLFOX6 (HR=0.683, 95% CI: 0.529, 0.881).

Among the 283 patients randomised to receive VYLOY in combination with mFOLFOX6, the ORR (data cut-off September 2022) for patients with gastric adenocarcinoma was 46.6% (102/219) (95% CI: 39.8, 53.4) compared with placebo in combination with mFOLFOX6 with an ORR of 46.2% (97/210) (95% CI: 39.3, 53.2). The median duration of response (DOR) for VYLOY in combination with mFOLFOX6 and placebo in combination with mFOLFOX6 was 10.0 months (95% CI: 6.6, 10.3) and 7.4 months (95% CI: 6.2, 10.8), respectively.

Table 5. Exploratory subgroup analysis for White versus Asian patients with gastric adenocarcinoma in SPOTLIGHT (data cut-off September 2022)

	White (n = 182)		**Asian (n = 174)**	
	VYLOY with mFOLFOX6 (n = 101)	**Placebo with mFOLFOX6 (n = 81)**	**VYLOY with mFOLFOX6 (n = 85)**	**Placebo with mFOLFOX6 (n = 89)**
PFS				
Median (95% CI)	8.9 (8.2, 17.0)	9.4 (6.8, 12.7)	14.0 (12.3, 18.1)	8.2 (6.3, 9.1)
HR (95% CI)	0.869 (0.585, 1.291)		0.539 (0.349, 0.834)	
OS				
Median (95% CI)	17.3 (12.0, 23.8)	13.8 (10.8, 17.1)	23.8 (19.0, 28.7)	15.6 (12.2, 19.0)
HR (95% CI)	0.835 (0.568, 1.227)		0.601 (0.399, 0.907)	

A final analysis (updated PFS, final OS, data cut-off September 2023) for efficacy for the SPOTLIGHT study among patients with gastric adenocarcinoma demonstrated a median PFS (as assessed by IRC) of 12.4 months for VYLOY in combination with mFOLFOX6 compared to 8.7 months for placebo with mFOLFOX6 (HR=0.654, 95% CI: 0.508, 0.841) and a median OS for VYLOY in combination with mFOLFOX6 of 19.8 months versus 14.3 months for placebo with mFOLFOX6 (HR=0.721, 95% CI: 0.575, 0.905).

GLOW (8951-CL-0302)

The safety and efficacy of VYLOY in combination with CAPOX was evaluated in a phase 3, double-blind, randomised, multicentre study that enrolled 507 patients whose tumours were CLDN18.2 positive, HER2-negative, with locally advanced unresectable or metastatic gastric (n = 428) 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 VYLOY in combination with CAPOX (n=254) or placebo in combination with CAPOX (n=253). VYLOY 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 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 VYLOY and capecitabine at the discretion of the investigator, until progression of disease or unacceptable toxicity.

Patients were excluded from the study if they had a complete or partial gastric outlet syndrome, positive test for 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.

Treatment with VYLOY continued until RECIST v1.1-defined progression of disease as determined by IRC, unacceptable toxicity or subsequent anticancer treatment was initiated. Tumour assessments were performed every 9 weeks up to and including week 54, then every 12 weeks thereafter.

The primary efficacy outcome was PFS as assessed per RECIST v1.1 by IRC. The key secondary efficacy outcome was OS. Other secondary efficacy outcomes were ORR and DOR as assessed per RECIST v1.1 by IRC.

Among patients who received VYLOY or placebo in combination with CAPOX, the median age of patients included was 60 years (range: 21 to 83); 62% were male; 37% were White, 63% were

Asian. 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).

In patients with gastric adenocarcinoma, the median PFS (determined by an IRC, data cut-off October 2022) for VYLOY in combination with CAPOX was 8.3 months (95% CI:7.9,9.4) compared to 6.4 months (95% CI: 6.1, 8.1) for placebo in combination with CAPOX (HR=0.606, 95% CI:0.471, 0.780).

In patients with gastric adenocarcinoma, the median OS (data cut-off October 2022) for VYLOY in combination with CAPOX was 14.5 months (95% CI: 12.3, 17.2) compared to 12.1 months (95% CI: 9.9, 13.7) for placebo in combination with CAPOX (HR=0.731, 95% CI: 0.572, 0.934).

Among the 254 patients randomised to receive VYLOY in combination with CAPOX, the ORR for patients with gastric adenocarcinoma (data cut-off October 2022) was 42.9% (94/219) (95% CI: 36.3, 49.8) compared with placebo in combination with CAPOX with an ORR of 37.8% (79/209) (95% CI: 31.2, 44.8). The median DOR for VYLOY in combination with CAPOX and placebo in combination with CAPOX was 6.3 months (95% CI: 5.4, 8.5) and 6.0 months (95% CI: 4.3, 6.2), respectively.

Table 6. Exploratory subgroup analysis for White versus Asian patients with gastric adenocarcinoma in GLOW (Data cut-off October 2022)

	White (n = 148)		**Asian (n = 279)**	
	VYLOY with CAPOX (n = 77)	**Placebo with CAPOX (n = 71)**	**VYLOY with CAPOX (n = 142)**	**Placebo with CAPOX (n = 137)**
PFS				
Median (95% CI)	8.0 (6.6, 8.8)	7.8 (5.4, 8.3)	8.8 (7.8, 10.6)	6.1 (5.3, 7.9)
HR (95% CI)	0.830 (0.542, 1.272)		0.510 (0.372, 0.700)	
OS				
Median (95% CI)	13.6 (10.4, 18.2)	13.3 (8.5, 17.4)	15.5 (12.4, 17.6)	12.2 (9.3, 13.2)
HR (95% CI)	0.843 (0.549, 1.294)		0.684 (0.507, 0.924)	

A final analysis (updated PFS, final OS, data cut-off January 2024) for efficacy for the GLOW study among patients with gastric adenocarcinoma demonstrated a median PFS (as assessed by IRC) of 8.3 months for VYLOY in combination with CAPOX versus 6.4 months for placebo with CAPOX (HR=0.619, 95% CI: 0.487, 0.787) and a median OS for VYLOY in combination with CAPOX of 14.3 months compared to 11.8 months for placebo with CAPOX (HR=0.715, 95% CI: 0.571, 0.894).

Pharmacokinetics

The pharmacokinetics of zolbetuximab was determined in a model analysis of the population pharmacokinetics for which pooled data of 714 patients in 8 studies in phase I, II and III who received intravenous VYLOY were considered.

Absorption

Not applicable.

Distribution

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 18 weeks with a mean (SD) C_{max} and AUC_{tau} at 425 (91) µg/mL and 3359 (1254) day•µg/mL, respectively. Based on simulation analyses, with the administration of a dose of 800/400 mg/m^2 every two weeks, the steady state is expected to be achieved by 16 weeks with a mean (SD) C_{max} and AUC_{tau} at 326 (74) µg/mL and 3349 (1250) day•µg/mL, respectively.

The simulation analyses also indicate that the administration of a dose of 800/400 mg/m² every 2 weeks results in 23% lower C_{max} at steady state and 10% higher C_{min} values at steady state, compared to the respective values after administration of a dose of 800/600 mg/m² every 3 weeks.

The estimated mean steady state volume of distribution of zolbetuximab was 16.4 L. A mean accumulation of 1.53 was estimated for AUC_{tau} with no accumulation expected for C_{max}.

Metabolism

No metabolism study was conducted for zolbetuximab in consideration of the biological nature of the molecule. Zolbetuximab is expected to be catabolised into small peptides and amino acids.

Elimination

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

Kinetics in specific patient groups

Hepatic impairment

Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GEJ adenocarcinomas, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified in patients with mild hepatic impairment as measured by total bilirubin (TB) and aspartate aminotransferase (AST) (TB ≤ upper limit of normal (ULN) and AST > ULN, or TB > 1 to 1.5 x 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 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).

Renal impairment

Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GEJ adenocarcinomas, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified in patients with mild [creatinine clearance (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 (C-G) formula. Zolbetuximab has only been evaluated in a limited number of patients with severe renal impairment (CrCL ≥15 to <30 mL/min; n=1).

Elderly patients

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% White, 42.2% Asian, 4.2% Missing, 2.7% Others, and 0.8% Black].

Children and adolescents

The pharmacokinetics of zolbetuximab in paediatric patients has not been evaluated.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and reproductive toxicity. No studies in animals have been performed to evaluate carcinogenicity or mutagenicity.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except with 0.9% sodium chloride solution. Do not co-administer other drugs through the same infusion line.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after dilution/reconstitution

Reconstituted concentrate in the vial:

Reconstituted vials may be stored at room temperature (≤ 30°C) for up to 6 hours.

Do not freeze.

Do not expose to direct sunlight.

Discard unused vials with reconstituted concentrate beyond the recommended storage time.

Diluted dosing solution in the infusion bag:

From a microbiological point of view, after dilution into the infusion bag, the diluted solution in the bag should be administered immediately. If not administered immediately, the prepared infusion bag should be stored (the holding time, inclusive the infusion time, may not exceed 24 hours in total):

- 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
  OR
- at room temperature (≤ 30°C) for no longer than 12 hours including infusion time from when the prepared infusion bag is removed from the refrigerator.

Do not freeze.

Do not expose to direct sunlight.

Discard unused prepared infusion bags beyond the recommended storage time.

Special precautions for storage of unopened vials

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original packaging. Keep the container in the outer carton in order to protect the contents from light.

Instructions for handling

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 content of the vial by slowly adding 5.0 mL of sterile water for injection (SWFI). Direct the stream of SWFI along the wall of the vial and not directly onto the lyophilised powder. The reconstituted concentrate contains 20 mg/mL of zolbetuximab.
5. Slowly swirl each vial until the contents are completely dissolved. Allow the content of 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 discolouration. The reconstituted concentrate should be clear to slightly opalescent, colourless to slight yellow and free of visible particles. Discard any vial with visible particles or discolouration in the concentrate.
7. Based upon the calculated dose amount, the reconstituted concentrate 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 "*Shelf life after dilution/reconstitution*" for storage of reconstituted vials.

Dilution in infusion bag

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

   The final diluted dosing solution of zolbetuximab 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 tubings 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. Discard any unused portion left in the single-dose vials.

Administration

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

14. Immediately administer the infusion according to the infusion rates presented in Table 3 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].

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

16. If not administered immediately, refer to "*Shelf life after dilution/reconstitution*" for storage of the prepared infusion bag.

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

Authorisation number

69501 (Swissmedic)

Packs

VYLOY 100 mg glass vials, 20 mm aluminium seal with a green cap, in cartons containing 1 and 3 vials. [A]

Marketing authorisation holder

Astellas Pharma AG, 8304 Wallisellen, Switzerland

Date of revision of the text

December 2024