Unit: Technical Assessment Unit

Assessment report

Vyloy®

Administrative information:

Trade name of the medicinal product:	Vyloy 100mg
INN (or common name) of the active substance(s):	Zolbetuximab
Manufacturer of the finished product	Simtra - Germany
Marketing Authorization holder	Astellas Pharma Europe B.V., Sylviusweg 62, 2333 BE LEIDEN- The Netherlands
Applied Indication(s):	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-esophageal junction (GEJ) adenocarcinoma whose tumors are Claudin (CLDN) 18.2 positive
Pharmaceutical form(s) and strength(s):	- Lyophilized powder for Concentrate for solution for I.V infusion - After reconstitution, each ml contains 20 mg.
Route of administration	IV INFUSION
Registration track	EMA approved

List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
AUC	Area under the concentration curve
CAPOX	Capecitabine plus Oxaliplatin
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
CLDN18.2.	Claudin-18 splice variant 2
Cmax	peak serum concentration
DNA	deoxyribonucleic acid
EFD	Embryo-Fetal Development
EOF	Epirubicin, 5-Fluorouracil And 5-Fluorouracil
EOX	Epirubicin, Oxaliplatin, and Capecitabine
FLO	5-Fluorouracil, leucavorin and 5-Fluorouracil
FO	5-Fluorouracil and Oxaliplatin
GEJ	Gastroesophageal Junction
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
IgG1	Immunoglobulin G subclass 1
IMAB362	Zolbetuximab
mFOLFOX6	Modified Fluorouracil, Leucovorin, and Oxaliplatin
NOAEL	No observed adverse effect level
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
Q3W	Every 3 Weeks
TEAE	Treatment-Emergent Adverse Event

Dossier initial submission and evaluation process:

-The file evaluated according to EDA regulation based on reliance pathway (Reliance level 2), the company submitted Complete CTD file.

1. Introduction

1. Zolbetuximab (formerly known as IMAB362) is a novel investigational chimeric (mouse/human) immunoglobulin G subclass 1 antibody produced in Chinese Hamster Ovary cells by standard recombinant expression technology. Zolbetuximab is directed against the tight junction protein, claudin-18 splice variant 2 (CLDN18.2), a transmembrane protein that in healthy tissue is expressed exclusively on gastric epithelial cells in the pit and base regions of the gastric glands. CLDN18.2 is expressed in primary gastric, esophageal and pancreatic adenocarcinomas and is maintained in the course of malignant transformation.

2. Astellas is developing zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy 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 tumors are CLDN18.2 positive, which is the focus of this BLA.

3. Zolbetuximab is supplied with 100 mg/vial and 300 mg/vial presentations as a lyophilized powder for solution for infusion. The vial contains 105 mg and 315 mg zolbetuximab and 100 mg and 300 mg can be extracted, resulting in 100 mg/vial and 300 mg/vial, respectively.

2. <u>Quality aspects:</u>

- **Manufacturer(s):**

- **Drug Substance**

- The Active substance is manufactured at. Patheon - USA.

- **Drug product**

- The Finished product is manufactured at Simtra - Germany.

-Manufacturing of both DS and DP are performed in accordance with cGMP regulations.

- **Stability**

Drug substance:

- Approved Storage Conditions of the active substance: (≤ - 60°C)

-Approved shelf life for the active substance: 48 months

Drug product:

-Approved Storage Conditions of the finished product:

Finished product:

-Store in a refrigerator (2 – 8 ºC).

-Do not freeze.

-Store in the original package in order to protect from light

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.

- Slowly swirl until the contents are completely dissolved, do not shake the vial.

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.

-Approved shelf life for the finished product: 48 months

3. Non–clinical aspect

Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer death worldwide. In 2020, there were an estimated 1.1 million new cases and approximately 770000 deaths worldwide from gastric cancer. Incidence and mortality of gastric cancer is about 2-fold higher in males vs females. Eastern Asia (primarily China) comprises about 60% of the global cases of gastric cancer.

CLDN18.2 is a member of the CLDN family that is involved in the formation of tight junctions in epithelia and endothelia. Tight junctions are essential for the sealing of the cellular sheets forming a luminary barrier and controlling paracellular ion flux. CLDN18.2 is expressed in a diversity of human cancers and is the dominant isoform in gastric cancer. The expression of CLDN18.2 is present in 74% to 87% of primary gastric adenocarcinomas. Furthermore, 78% of esophageal adenocarcinomas display expression of CLDN18.2.

Zolbetuximab (also known as IMAB362) is a chimeric (mouse/human) IgG1 antibody directed against the tight junction molecule CLDN18.2. CLDN18.2 is a highly tissue specific cell surface molecule that is expressed in normal gastric tissue as well as in many human cancers.

Zolbetuximab was generated by recombinant DNA technology and gene synthesis by joining mouse variable regions obtained from a CLDN18.2-specific murine hybridoma clone to human antibody kappa light and IgG1 heavy chain constant regions. Antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) are the identified modes of action mediated by the Fc region of zolbetuximab.

Pharmacology:

- Zolbetuximab primary pharmacodynamics was characterized by a series of studies evaluating target binding to human, mouse and cynomolgus monkey CLDN18.2, mechanism of action, in vivo tissue selectivity and in vivo antitumor activity. The effects of zolbetuximab in combination with chemotherapy were also investigated in vitro and in vivo.
- In vitro functional studies have demonstrated that zolbetuximab mediates Fc-dependent cytotoxic activity against target cells expressing CLDN18.2. Zolbetuximab induced both ADCC and CDC. In addition, zolbetuximab was found to induce tumour cell apoptosis. The anti-tumour activity of zolbetuximab in combination chemotherapy was also evaluated. The different chemotherapeutic regimens (EOF, FLO, FO) are considered representative of the classes of therapeutics used clinically for treatment of gastric or GEJ cancers. In vivo anti-tumour activity of zolbetuximab was evaluated in mouse xenograft models of human gastric cancer. Zolbetuximab monotherapy slowed tumour growth compared to that in saline-treated animals; survival of zolbetuximab-treated mice was minimally prolonged. Consequently, the in vivo anti-tumour efficacy of zolbetuximab was tested in combination with chemotherapeutic agents. In immunocompetent mice bearing murine, CLDN18.2-positive gastric tumours, the zolbetuximab/chemotherapy combination treatment induced significantly enhanced tumour growth inhibition and also prolonged survival compared to the monotherapy group.
In tumours from the combination therapy group, an increase in percent infiltrating CD8+ T cells was observed.
- No test article-related effects on central nervous system, cardiovascular system or respiratory system were noted.

Pharmacokinetics:

- A single dose PK study in cynomolgus monkeys was conducted in order to compare the PK parameters from two different zolbetuximab drug substances manufactured at different sites. No difference was noted in PK parameters or ADA production among the groups, indicating that the PK profile is comparable, although somewhat limited given the small number of animals.

Toxicology:

- In single dose toxicity studies, mice were administered up to 100 mg/kg zolbetuximab intravenously. Zolbetuximab was well tolerated. In addition, in a dose escalation toxicity study in cynomolgus monkeys, the animals received up to 150 mg/kg zolbetuximab, no signs of toxicity were noted.

- No toxicity or zolbetuximab-related adverse effects were 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).
- An almost dose proportional increase of Cmax and AUC was observed. No differences between the sexes or marked accumulation was noted. ADAs were present in some animals but obviously did not significantly influence the exposure to the test article.
- Zolbetuximab is intended for the treatment of patients with advanced cancer. Therefore, in accordance with ICH S9, dedicated studies to assess the fertility and early embryonic development to implantation and the effects on pre- and postnatal development including maternal function were not conducted. Furthermore, male and female reproductive organs were examined microscopically in repeat dose toxicity studies in mice and cynomolgus monkeys. No histopathological findings were noted in reproductive organs in either study.
The maternal and foetal NOAEL in the EFD study is 300 mg/kg, the highest dose administered.
- Since vomiting and nausea were observed in clinical studies of zolbetuximab, mechanistic studies were conducted to assess emetic potential using ferrets. Results confirmed that zolbetuximab causes cellular damage to the gastric mucosa, resulting in retching and vomiting. Antiemetic medication somehow alleviated the symptoms, but a clear effect was not demonstrated since clinical signs and histopathology was very individual. These studies are considered unnecessary, since vomiting as side effect is not surprising given the mechanism of action of zolbetuximab.

- Tissue cross reactivity studies with zolbetuximab or murine surrogates were conducted with human, mouse or cynomolgus monkey tissue and confirmed restricted CLDN18.2 expression in the stomach. No unexpected binding was noted.

Overall conclusion: no issues for concern regarding the data submitted for zolbetuximab from the non-clinical point of view.

1. **Clinical aspect:**

Zolbetuximab (IMAB362; Vyloy®) is a monoclonal antibody directed against Claudin 18.2 (CLDN18.2), a tight junction protein selectively expressed in gastric and gastroesophageal junction (GEJ) adenocarcinomas. The clinical development program for zolbetuximab comprises nine clinical studies, including four completed Phase I studies, three Phase II studies (two completed and one ongoing), and two pivotal Phase III randomized controlled trials.

The program was designed to comprehensively evaluate clinical pharmacology, efficacy, immunogenicity, and safety of zolbetuximab as monotherapy and in combination with

standard fluoropyrimidine- and platinum-based chemotherapy regimens. Particular focus was placed on first-line treatment of CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric and GEJ adenocarcinoma, a population with high unmet medical need.

Clinical Efficacy and Immunogenicity

Clinical Efficacy

- Early-Phase Evidence (Phase I–II)

Phase I studies established the recommended dosing regimen (800 mg/m² loading dose followed by 600 mg/m² Q3W) and demonstrated preliminary antitumor activity across Western, Japanese, and Chinese populations. Phase II studies (MONO, FAST, and ILUSTRO) provided evidence of dose-dependent antitumor activity, both as monotherapy and in combination with chemotherapy and immune checkpoint inhibitors.
The FAST study demonstrated a clinically meaningful improvement in progression-free survival (PFS) when zolbetuximab was combined with EOX chemotherapy compared with chemotherapy alone, supporting progression to pivotal Phase III trials.

- Pivotal Phase III Studies

Two global, randomized, double-blind, placebo-controlled Phase III trials were conducted:
SPOTLIGHT (Study 8951-CL-0301): zolbetuximab + mFOLFOX6
GLOW (Study 8951-CL-0302): zolbetuximab + CAPOX
Both studies enrolled patients with CLDN18.2-positive (≥75% tumor cells), HER2-negative gastric or GEJ adenocarcinoma in the first-line setting.
Primary Endpoint: Progression-Free Survival (PFS)
SPOTLIGHT
Median PFS: 11.0 vs 8.9 months
HR: 0.734 (95% CI: 0.591–0.910); p = 0.0024
GLOW
Median PFS: 8.2 vs 6.8 months
HR: 0.689 (95% CI: 0.552–0.860); p = 0.0005
Consistent PFS benefit was observed across predefined subgroups, including metastatic and locally advanced disease.
Overall Survival (Key Secondary Endpoint)
SPOTLIGHT
Median OS: 18.2 vs 15.6 months
HR: 0.784 (95% CI: 0.644–0.954); p = 0.0075
GLOW
Median OS: 14.3 vs 12.2 months
HR: 0.763 (95% CI: 0.622–0.936); p = 0.0047

These findings demonstrate clinically meaningful and statistically significant improvements in survival outcomes when zolbetuximab is added to standard chemotherapy.

Immunogenicity
Across Phase II and III studies, immunogenicity incidence was low, with no clinically meaningful impact on pharmacokinetics, efficacy, or safety. Hypersensitivity and anaphylactic reactions were infrequent and manageable with standard risk mitigation strategies.

Clinical Safety
Safety was evaluated using integrated data from Phase II and Phase III studies, with primary analyses from SPOTLIGHT and GLOW.
Overall Safety Profile, nearly all patients experienced at least one TEAE, reflecting the advanced disease setting and intensive chemotherapy backbone.
The overall incidence of Grade ≥3 TEAEs, serious TEAEs, and TEAEs leading to death was comparable between zolbetuximab and control arms.
Key Safety Findings:
Gastrointestinal Toxicity: Zolbetuximab was associated with increased rates of nausea, vomiting, and decreased appetite, particularly during early cycles.
Grade ≥3 nausea and vomiting occurred in 11.6% and 13.6% of patients, respectively.
These events were generally manageable through infusion rate modification and supportive care.
Hematologic Toxicity: Rates of anemia, neutropenia, and thrombocytopenia were consistent with chemotherapy-related toxicity and similar between treatment arms.
Thromboembolic Events: A numerical imbalance in thrombotic events was observed (24.4% vs 17.8%); however:
Events were heterogeneous: Confounding factors (advanced malignancy, comorbidities) were present
No clear causal relationship with zolbetuximab was established
Hypersensitivity Reactions: Serious hypersensitivity reactions occurred in ~3–4% of patients
Anaphylaxis was rare (≤0.5%) and led to permanent discontinuation in 0.3% of cases
Mortality: TEAE-related deaths were comparable between arms. Most deaths were attributed to disease progression.

Benefit-Risk Analysis
Zolbetuximab demonstrated robust and clinically meaningful improvements in progression-free and overall survival in a molecularly defined population with limited therapeutic options. The magnitude and consistency of benefit across two independent pivotal trials strongly support its efficacy.

While treatment is associated with increased gastrointestinal toxicity, these adverse events are generally reversible, manageable, and occur early, allowing for proactive mitigation strategies. No new safety signals were identified that would outweigh the demonstrated survival benefit.
Considering the poor prognosis of CLDN18.2-positive gastric and GEJ adenocarcinoma, the overall benefit–risk profile of zolbetuximab in combination with fluoropyrimidine- and platinum-based chemotherapy is favorable.

Overall Conclusion
The clinical development program for zolbetuximab provides substantial and consistent evidence of efficacy in CLDN18.2-positive, HER2-negative gastric and GEJ adenocarcinoma. The pivotal Phase III SPOTLIGHT and GLOW trials demonstrated statistically significant and clinically meaningful improvements in both progression-free and overall survival, establishing zolbetuximab as an effective first-line therapeutic option.

The safety profile is well characterized and manageable, with predictable gastrointestinal toxicity and no evidence of unacceptable long-term risk. Taken together, the totality of evidence supports a positive benefit-risk balance for zolbetuximab in its proposed indication.

5. General Conclusion and Recommendations if any:
Based on the review of CTD modules and other supplementary documents, the product is approved.

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/vyloy-epar-public-assessment-report_en.pdf