VYLOY™ (zolbetuximab) Dosing and Adverse Event Management Guide

Indication

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

Adverse events should be reported. You can report adverse events directly via the Yellow Card Scheme at https://yellowcardmhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting adverse events, you can help provide more information on the safety of this medicine.

This material is intended for UK Healthcare Professionals only.
Please see Important Safety Information on pages 22–26.
Prescribing information for VYLOY™ (zolbetuximab) can be found on page 27.

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VYLOY™ zolbetuximab for infusion 100mg vial

Focusing on helping you support patients

Use this guide to learn about administering VYLOY (zolbetuximab) to your patients and how to support them throughout treatment.

In the following pages, you'll find out about:

Dosing and administration of VYLOY (zolbetuximab)

Understanding possible adverse events

Hypersensitivity/ infusion-related reactions

Treating nausea and vomiting

Table of Contents

VYLOY™
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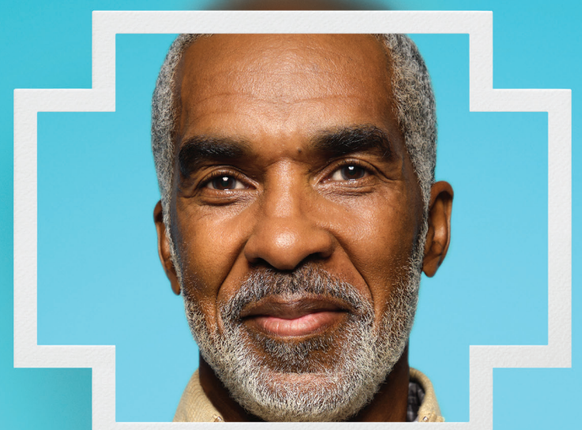
01 About VYLOY (ZOLBETUXIMAB)



VYLOY (zolbetuximab) is a first-in-class CLDN18.2-directed monoclonal antibody for HER2-negative, advanced* G/GEJ adenocarcinoma[1–3]

Based on 2 global phase 3 clinical trials, it is estimated that:

42% **OF PATIENTS** with HER2-negative advanced* G/GEJ adenocarcinoma are CLDN18.2-positive and may be candidates for VYLOY (zolbetuximab) + chemotherapy[1–3†‡]

VYLOY (zolbetuximab) was studied in combination with mFOLFOX6 or CAPOX in 2 phase 3 clinical trials

Both trials (SPOTLIGHT and GLOW) included PFS (primary endpoint) and overall survival (key secondary endpoint) in evaluating VYLOY (zolbetuximab) + chemotherapy‡ versus chemotherapy alone.[1]

The **12-month PFS rate** in the SPOTLIGHT and GLOW trials, were **48.9%** and **34.9%** in the VYLOY (zolbetuximab) + chemotherapy group compared with 35.0% and 19.1% in the placebo groups, respectively.[1]

*Locally advanced unresectable or metastatic; †CLDN18.2-positive is defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 staining by IHC;[2,3] ‡Fluoropyrimidine- and platinum-containing chemotherapy.

CAPOX, capecitabine and oxaliplatin; **CLDN18.2**, claudin 18.2; **G/GEJ**, gastric/gastro-oesophageal junction; **IHC**, immunohistochemistry; **mFOLFOX6**, modified leucovorin (folinic acid), fluorouracil and oxaliplatin; **PFS**, progression-free survival.

LEARN MORE ABOUT VYLOY (ZOLBETUXIMAB) AND EXPLORE RESULTS FROM 2 PHASE 3 CLINICAL TRIALS (SPOTLIGHT AND GLOW) AT [VYLOYhcp.COM]

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02 Dosing and Administration

VYLOY (zolbetuximab) infusion

VYLOY (zolbetuximab) can be administered every 2 or 3 weeks aligning with selected chemotherapy dosing schedule[1]

BEFORE THE FIRST INFUSION[1]
Symptoms of nausea and/or vomiting should be resolved to grade ≤1

PRE-TREATMENT[1]
Prior to each infusion, pre-treat patients with a combination of anti-emetics (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

Recommended dosage and infusion rates*[1]

Treatment cycle	VYLOY (zolbetuximab) dose	Rate of infusion
Cycle 1 (loading dose)	 **800mg/m²**	• Administer at 100mg/m²/hour for the first 30-60 minutes • In the absence of adverse reactions after 30-60 minutes, the rate of the infusion can be escalated to 200-400 mg/m²/hour • If an infusion-related reaction of grade 2 occurs, pause the infusion until grade ≤ 1 then resume at a reduced infusion rate for the remaining infusion • Consider pre-medication for next infusion • For grade 3 or 4 infusion-related reactions, immediately stop the infusion and permanently discontinue
Cycle 2 onward (maintenance dose) 3-weekly dosing regimen	 **600mg/m² every 3 weeks**	• Administer at 75mg/m²/hour for the first 30-60 minutes • In the absence of adverse reactions after 30-60 minutes, the rate of infusion can be escalated to 150–300mg/m²/hour • If an infusion-related reaction of grade 2 occurs, pause the infusion until grade ≤ 1 then resume at a reduced infusion rate for the remaining infusion • Consider pre-medication for next infusion • For grade 3 or 4 infusion-related reactions, immediately stop the infusion and permanently discontinue
	OR	
Cycle 2 onward (maintenance dose) 2-weekly dosing regimen	 **400mg/m² every 2 weeks**	• Administer at 50mg/m²/hour for the first 30-60 minutes • In the absence of adverse reactions after 30-60 minutes, the rate of infusion can be escalated to 100-200 mg/m²/hour • If an infusion-related reaction of grade 2 occurs, pause the infusion until grade ≤ 1 then resume at a reduced infusion rate for the remaining infusion • Consider pre-medication for next infusion • For grade 3 or 4 infusion-related reactions, immediately stop the infusion and permanently discontinue
Infusion must be over a minimum of 2 hours through an IV line		

Refer to the fluoropyrimidine- or platinum-containing chemotherapy Summary of Product Characteristics regarding the dosing information for chemotherapy.

*Administer VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy.[1]

IV, intravenous.

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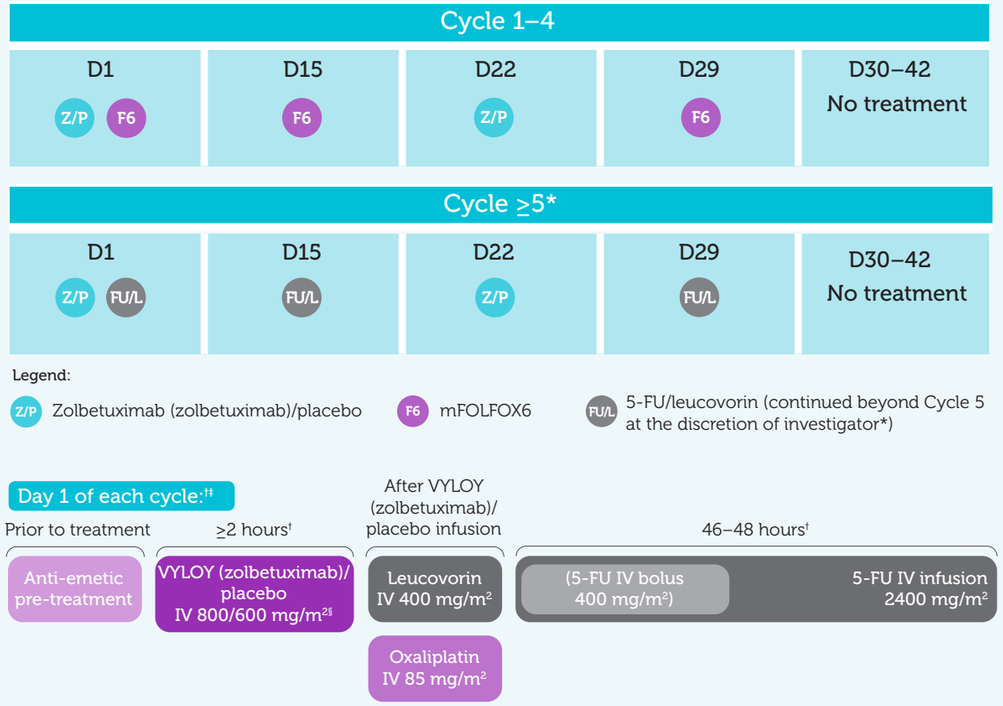
VYLOY (zolbetuximab) infusion

- In the absence of adverse reactions after 30-60 minutes, the infusion rate can be increased to the subsequent infusion rate as tolerated[1]
- If VYLOY (zolbetuximab) and chemotherapy* are administered on the same day, VYLOY (zolbetuximab) must be administered first[1]

*Fluoropyrimidine- and platinum-containing chemotherapy.[1]

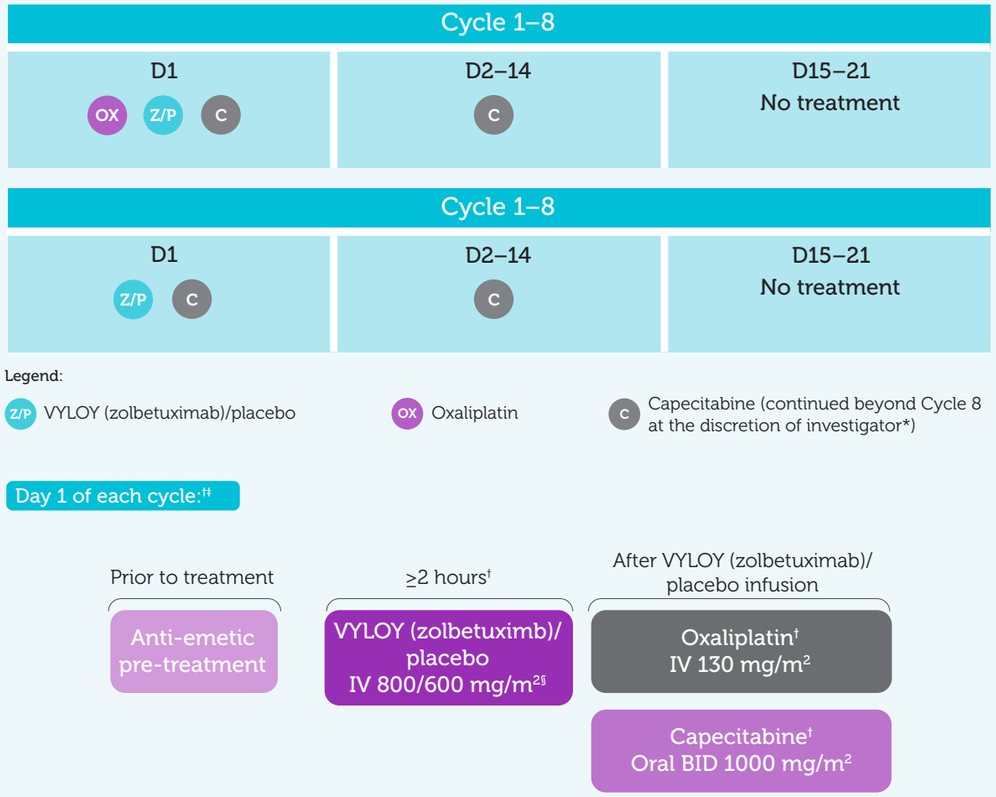
The infusions are started at a slower rate for the first 30-60 minutes to help mitigate potential adverse events. The rate can be increased for the remainder of the infusion as tolerated.

SPOTLIGHT: Treatment dosing regimen[1,2]



*Patients continued on VYLOY (zolbetuximab) and 5-FU/folinic acid until the patient met the study treatment discontinuation criteria; †Refer to the VYLOY (zolbetuximab) Summary of Product Characteristics for full dosing information. Refer to the fluoropyrimidine- or platinum-containing chemotherapy Summary of Product Characteristics regarding the dosing information for chemotherapy; ‡Either VYLOY (zolbetuximab)/placebo or chemotherapy is omitted on days when only VYLOY (zolbetuximab) (D22) or chemotherapy (D15, D29) alone is given; §VYLOY (zolbetuximab) 800mg/m² on Cycle 1 D1 followed by 600mg/m² on Cycle 1 D22 and D1 and D22 of subsequent cycles.
5-FU, fluorouracil; D, day; IV, intravenous; mFOLFOX6, leucovorin (folinic acid), fluorouracil, and oxaliplatin (modified regimen).

GLOW: Treatment dosing regimen[1,3]



*Patients continued on VYLOY (zolbetuximab) and capecitabine until the patient met the study treatment discontinuation criteria; †Refer to the VYLOY (zolbetuximab) Summary of Product Characteristics for full dosing information. Refer to the fluoropyrimidine- or platinum-containing chemotherapy Summary of Product Characteristics regarding the dosing information for chemotherapy; ‡VYLOY (zolbetuximab)/placebo and oxaliplatin were omitted on days when only capecitabine was given (D2, D14); §VYLOY (zolbetuximab) 800mg/m² on Cycle 1 D1 followed by 600mg/m² in subsequent cycles.
BID, twice daily; D, day; IV, intravenous.

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VYLOY (zolbetuximab) administration

Infusion timing

Prior to each infusion of VYLOY (zolbetuximab), pre-medicate patients with anti-emetics.[1]

2hr+

Immediately administer the infusion over a minimum of 2 hours through an IV line.
Do not administer as an IV push or bolus.[1]

If the infusion time exceeds the recommended storage time at room temperature (6 hours from end of preparation of infusion solution), the infusion bag must be discarded and a new infusion bag prepared to continue the infusion.

Infusion line considerations[1]

- In-line filters (pore size of 0.2 micron with materials listed in the Summary of Product Characteristics) are recommended to be used during administration
- Do not coadminister other drugs through the same infusion line
- **No incompatibilities** have been observed with closed system transfer device or central port composed of certain materials (see Summary of Product Characteristics for more details)

IV, intravenous.

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03 Adverse Event Management

Adverse events in clinical trials

Recognising potential adverse events[1]

In the clinical trials, adverse events that are listed as very common include nausea, vomiting, decreased appetite, hypoalbuminaemia and oedema peripheral.

SPOTLIGHT: Adverse events[2]

Adverse events (any grade) reported in ≥15% of patients in either treatment arm

TEAEs[2]	VYLOY (zolbetuximab) + mFOLFOX6 (n=279)		PLACEBO + mFOLFOX6 (n=278)	
	ANY GRADE, n (%)	GRADE ≥3, n (%)	ANY GRADE, n (%)	GRADE ≥3, n (%)
Any adverse event	278 (>99)	242 (87)	277 (>99)	216 (78)
Nausea	230 (82)	45 (16)	169 (61)	18 (6)
Vomiting	188 (67)	45 (16)	99 (36)	16 (6)
Decreased appetite	131 (47)	16 (6)	93 (33)	9 (3)
Diarrhoea	110 (39)	12 (4)	122 (44)	9 (3)
Peripheral sensory neuropathy	106 (38)	11 (4)	118 (42)	15 (5)
Neutropaenia	102 (37)	79 (28)	94 (34)	65 (23)
Anaemia	100 (36)	24 (9)	104 (37)	29 (9)
Constipation	99 (35)	3 (1)	112 (40)	2 (1)
Neutrophil count decrease	95 (34)	69 (25)	91 (33)	69 (25)
Fatigue	78 (28)	17 (6)	91 (33)	14 (5)
Asthenia	74 (27)	20 (7)	64 (23)	7 (3)
Abdominal pain	67 (24)	12 (4)	82 (29)	6 (2)
Stomatitis	58 (21)	7 (3)	57 (21)	3 (1)
Weight decreased	55 (20)	5 (2)	54 (19)	2 (1)
Pyrexia	54 (19)	1 (<1)	48 (17)	1 (<1)
White blood cell count decrease	50 (18)	8 (3)	46 (17)	16 (6)
Hypokalaemia	50 (18)	16 (6)	41 (15)	10 (4)
Oedema peripheral	49 (18)	2 (1)	26 (9)	0
Aspartate aminotransferase level increase	49 (18)	4 (1)	44 (16)	7 (3)
Abdominal pain upper	47 (17)	4 (1)	32 (12)	0
Paraesthesia	44 (16)	6 (2)	46 (17)	4 (1)
Hypoalbuminaemia	43 (15)	11 (4)	17 (6)	2 (1)
Dysgeusia	41 (15)	1 (<1)	40 (14)	0
Platelet count decrease	40 (14)	3 (1)	49 (18)	6 (2)
Alanine aminotransferase level increase	34 (12)	2 (1)	47 (17)	7 (3)
Thrombocytopaenia	28 (10)	4 (1)	45 (16)	4 (1)

Median duration of exposure to VYLOY (zolbetuximab) in combination with mFOLFOX6 was 6.2 months[2]

See page 15 for details on infusion rate adjustments for adverse reaction treatment.

mFOLFOX6, modified leucovorin (folinic acid), fluorouracil and oxaliplatin;
TEAE, treatment-emergent adverse event.

Please see Important Safety Information on pages 22–26, and accompanying full Summary of Product Characteristics.

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GLOW: Adverse events[3]

Adverse events (any grade) reported in ≥15% of patients in either treatment arm

TEAEs[3]	VYLOY (zolbetuximab) + CAPOX (n=254)		PLACEBO + CAPOX (n=249)	
	ANY GRADE, n (%)	GRADE ≥3, n (%)	ANY GRADE, n (%)	GRADE ≥3, n (%)
Any adverse event	251 (98.8)	185 (72.8)	244 (98.0)	174 (69.9)
Nausea	174 (68.5)	22 (8.7)	125 (50.2)	6 (2.4)
Vomiting	168 (66.1)	31 (12.2)	77 (30.9)	9 (3.6)
Decreased appetite	105 (41.3)	17 (6.7)	84 (33.7)	4 (1.6)
Anaemia	90 (35.4)	27 (10.6)	91 (36.5)	28 (11.2)
Diarrhoea	80 (31.5)	15 (5.9)	86 (34.5)	18 (7.2)
Neutrophil count decrease	70 (27.6)	26 (10.2)	59 (23.7)	24 (9.6)
Aspartate aminotransferase level increase	63 (24.8)	6 (2.4)	72 (28.9)	7 (2.8)
Platelet count decrease	61 (24.0)	19 (7.5)	60 (24.1)	20 (8.0)
Hypoalbuminaemia	57 (22.4)	8 (3.1)	35 (14.1)	4 (1.6)
Peripheral sensory neuropathy	56 (22.0)	1 (0.4)	56 (22.5)	6 (2.4)
White blood cell count decrease	51 (20.1)	5 (2.0)	39 (15.7)	9 (3.6)
Neutropaenia	50 (19.7)	18 (7.1)	35 (14.1)	7 (2.8)
Weight decreased	50 (19.7)	1 (0.4)	25 (10.0)	1 (0.4)
Alanine aminotransferase level increase	48 (18.9)	2 (0.8)	52 (20.9)	7 (2.8)
Palmar–plantar erythrodysesthesia	41 (16.1)	4 (1.6)	49 (19.7)	9 (3.6)
Abdominal pain	40 (15.7)	1 (0.4)	54 (21.7)	4 (1.6)
Constipation	39 (15.4)	–	52 (20.9)	–
Fatigue	34 (13.4)	7 (2.8)	42 (16.9)	9 (3.6)

Median duration of exposure to VYLOY (zolbetuximab) was 6.4 months[3]

See page 15 for details on infusion rate adjustments for adverse reaction treatment.

CAPOX, capecitabine and oxaliplatin; **TEAE**, treatment-emergent adverse event.

In the integrated safety analysis of hypersensitivity and infusion-related reactions:[1]

- All grade **hypersensitivity reactions** occurred in 1.6% (10/631) of patients treated with VYLOY (zolbetuximab) in combination with fluoropyrmidine and platinum-containing chemotherapy compared with 1.6% (10/611) in the placebo arm; severe (grade 3) reactions occured in 0.5% (3/631) of patients in the VYLOY (zolbetuximab) arm versus 0.3% (2/611) in the placebo arm
- All grade **infusion-related reactions** occured in 3% (19/631) of patients treated with VYLOY (zolbetuximab) in combination with fluoropyrmidine and platinum-containing chemotherapy compared with 1.1% (7/611) in the placebo arm; severe (grade 3) reactions occured in 0.5% (3/631) of patients in the VYLOY (zolbetuximab) arm versus 0% (0/611) in the placebo arm

VYLOY (zolbetuximab) adverse event management[1]

No dose reduction for VYLOY (zolbetuximab) is recommended. Adverse events for VYLOY (zolbetuximab) are managed by reducing the infusion rate, interrupting (pausing) infusion, withholding the dose and/or permanently discontinuing treatment as outlined in the table below.

Adverse reaction	Severity	Dose modification
Hypersensitivity reactions	Anaphylactic reactions, suspected anaphylaxis, grade 3 or 4	Immediately stop the infusion and permanently discontinue.
	Grade 2	• Pause the infusion until grade ≤1, then resume at a reduced infusion rate for the remaining infusion • For the next infusion, pre-medicate and administer per the infusion rates in Table 3 in the Summary of Product Characteristics
Infusion-related reactions	Grade 3 or 4	Immediately stop the infusion and permanently discontinue.
	Grade 2	• Pause the infusion until grade ≤1, then resume at a reduced infusion rate for the remaining infusion • For the next infusion, pre-medicate and administer per the infusion rates in Table 3 in the Summary of Product Characteristics
Nausea	Grade 2 or 3	• Pause the infusion until grade ≤1, then resume at a reduced infusion rate for the remaining infusion • For the next infusion, pre-medicate and administer per the infusion rates in Table 3 in the Summary of Product Characteristics
Vomiting	Grade 4	Permanently discontinue.
	Grade 2	• Pause the infusion until grade ≤1, then resume at a reduced infusion rate for the remaining infusion • For the next infusion, pre-medicate and administer per the infusion rates in Table 3 in the Summary of Product Characteristics

- In the combined analysis of the SPOTLIGHT and GLOW trials, the infusion rate was reduced for VYLOY (zolbetuximab) or mFOLFOX6/CAPOX in:[1]
  - 1 patient (0.2%) due to drug hypersensitivity
  - 1 patient (0.2%) due to an infusion-related reaction
  - 59 patients (9.4%) due to nausea and 49 patients (7.8%) due to vomiting
- Toxicity was graded per NCI CTCAE v5.0 in which grade 1 is mild, grade 2 is moderate, grade 3 is severe and grade 4 is life-threatening

CAPOX, capecitabine and oxaliplatin; **mFOLFOX6**, modified leucovorin (folinic acid), fluorouracil and oxaliplatin; **NCI CTCAE v5.0**, National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

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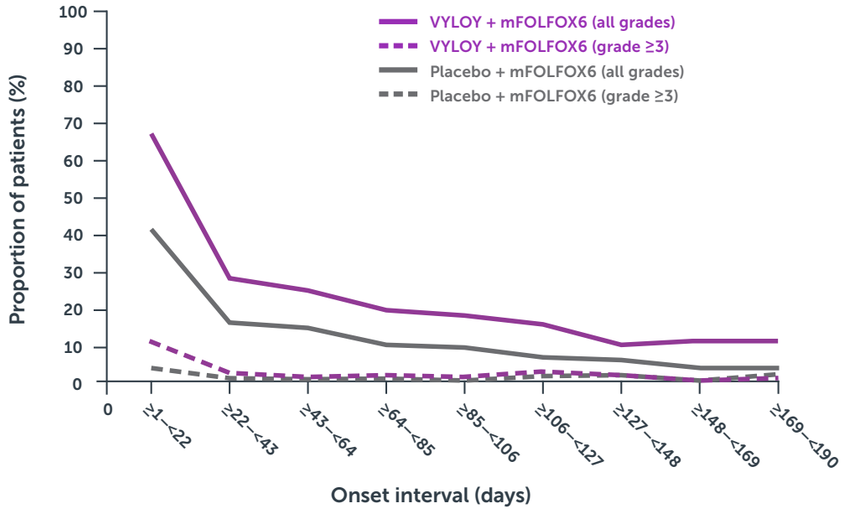
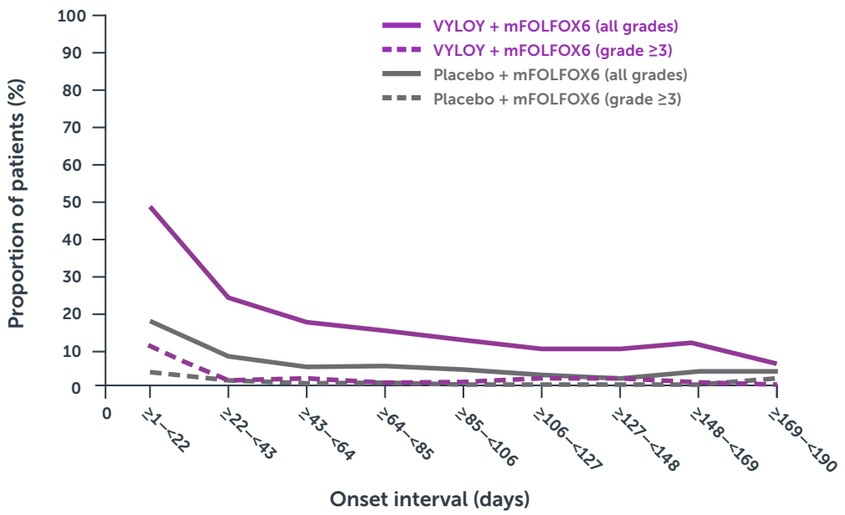
In the SPOTLIGHT and GLOW clinical studies, nausea and vomiting:

- Were the most common adverse events when VYLOY (zolbetuximab) was given with mFOLFOX6 or CAPOX (majority were grades 1 and 2)
- Were managed by infusion rate modifications, infusion interruptions and the use of anti-emetics[2,3]
- Occurred more often in the first cycle but decreased in incidence with subsequent cycles[1,4]

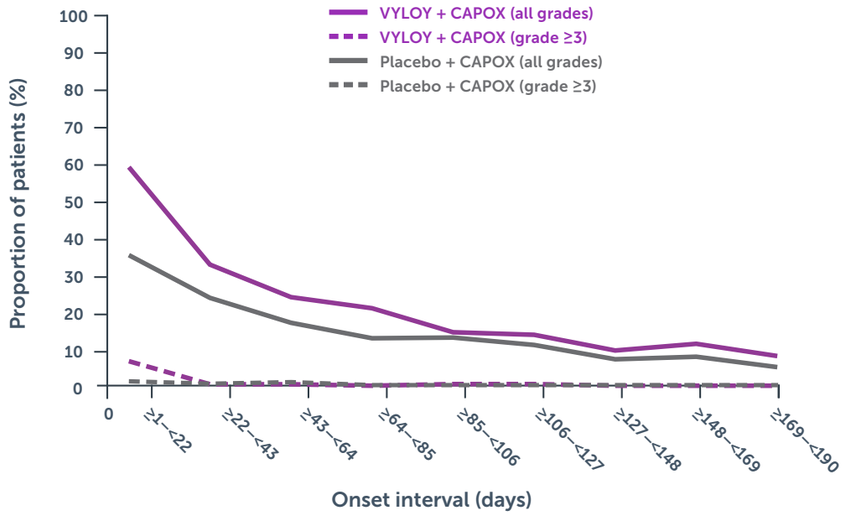
Nausea: All occurrences in SPOTLIGHT[4]



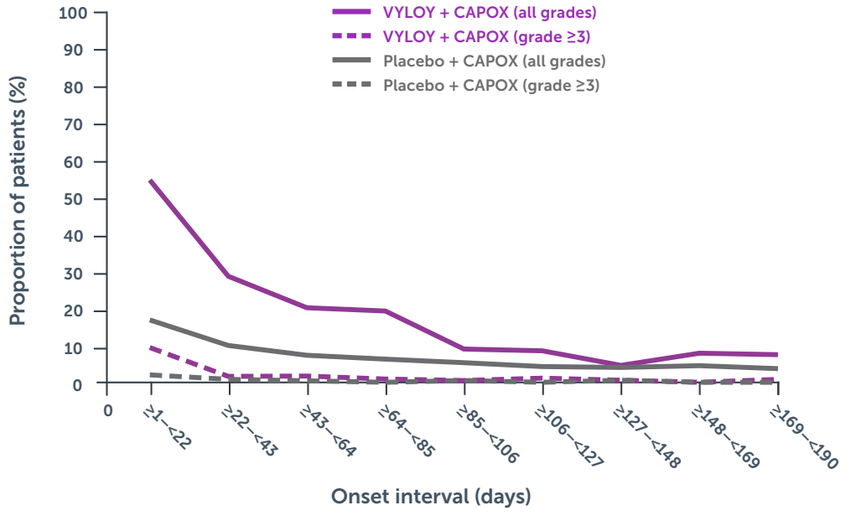
Vomiting: All occurrences in SPOTLIGHT[4]



Nausea: All occurrences in GLOW[3]



Vomiting: All occurrences in GLOW[3]



A substantial proportion of patients experienced grade 1 or 2 nausea or vomiting several weeks after first infusion. Monitor and manage using standard of care (including anti-emetic regimen or fluid replacement as per local protocols).[1]

Adverse event preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0. Nausea and vomiting have been confirmed as important identified risks. Adverse events, graded according to NCI CTCAE v4.03, were monitored throughout the trial and for 90 days after treatment discontinuation. Grade 4 nausea is not defined in CTCAE v4.03 and was determined and managed at the investigator's discretion. These data are not generalisable and cannot be used to predict adverse event outcomes. These data are from a phase 3 global randomised multicentre trial. The results presented are provided only as descriptive clinical information.

CAPOX, capecitabine and oxaliplatin; **mFOLFOX6**, modified leucovorin (folinic acid), fluorouracil and oxaliplatin; **NCI CTCAE v4.3**, National Cancer Institute Common Terminology Criteria for Adverse Events version 4.3.

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Treating nausea and vomiting

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

During or after infusion

Monitor and manage using standard of care (including anti-emetics or fluid replacement as clinically indicated).[1]

Other advice on anti-emetics[1]

GET PRESCRIPTION APPROVAL
so that anti-emetics are readily available (during infusion and at home)

REMIND PATIENTS TO TAKE
anti-emetics on time as prescribed

REMIND PATIENTS TO REFILL
their anti-emetic prescriptions

For more details, please refer to local anti-emetic protocols

TIP: Remind patients to tell their healthcare provider about all the medicines they take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Taking VYLOY (zolbetuximab) with certain other medicines may cause side effects.

This information is for informational purposes only and is not meant to replace the advice of a healthcare professional.

04 Storage and Handling

Shelf-life and special precautions for storage[1]

Prepared infusion bag
The following times include the administration period

Stored under refrigeration at 2°C to 8°C for no longer than 24 hours from the end of the preparation of the infusion bag. **Do not freeze**.

Stored at room temperature for no longer than 6 hours 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.

Reconstituted vials

Reconstituted vials may be stored at room temperature (≤30°C) for up to 5 hours.

Do not freeze.

Do not expose to direct sunlight.

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

05 Important Safety Information

Important Safety Information

Summary of the safety profile

The safety of VYLOY (zolbetuximab) was evaluated in 2 phase 2 studies (FAST, ILUSTRO) and 2 phase 3 studies (SPOTLIGHT, GLOW) in 631 patients who received at least 1 dose of VYLOY (zolbetuximab) 800 mg/m^2 as a loading dose followed by 600 mg/m^2 subsequent doses every 3 weeks in combination with fluoropyrimidine- and platinum-containing chemotherapy. The median duration of exposure to VYLOY (zolbetuximab) was 171 days (range: 1–1791 days). Serious adverse reactions occurred in 16% of patients treated with VYLOY (zolbetuximab). The most common serious adverse reactions (≥2%) were vomiting (4.3%) and nausea (3.6%).

19% of patients permanently discontinued VYLOY (zolbetuximab) due to adverse reactions; the most common adverse reactions (≥2%) leading to dose discontinuation were vomiting (3.8%) and nausea (3.3%). Adverse reactions leading to dose interruption of VYLOY (zolbetuximab) occurred in 60.4% of patients; the most common adverse reactions (≥2%) leading to dose interruption were vomiting (26.5%) and nausea (25.5%). The most common adverse reactions (≥2%) leading to dose rate reduction of the VYLOY (zolbetuximab) or fluoropyrimidine- and platinum-containing chemotherapy infusion were nausea (9.4%) and vomiting (7.8%).

Description of selected adverse reactions

In the integrated safety analysis, all grade hypersensitivity reactions such as anaphylactic reaction and drug hypersensitivity occurred in the VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy arm (0.5% [3/631], 1.6% [10/631]) compared with the placebo in combination with fluoropyrimidine- and platinum-containing chemotherapy arm [0.8% (0.8% [5/611], 1.6% [10/611]). Severe (grade 3) anaphylactic reaction and drug hypersensitivity occurred at a similar frequency in the VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy arm (0.5% [3/631], 0.2% [1/631]) compared with the placebo in combination with fluoropyrimidine- and platinum-containing chemotherapy arm (0.3% [2/611], 0.2% [1/611]). The median time to first onset of anaphylactic reaction or drug hypersensitivity with VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy was 22 days or 113 days, respectively. 2 (0.3%) patients permanently discontinued VYLOY (zolbetuximab) due to anaphylactic reaction. Dose interruption of VYLOY (zolbetuximab) was experienced due to drug hypersensitivity in 2 (0.3%) patients. The infusion rate was reduced for VYLOY (zolbetuximab) or fluoropyrimidine- and platinum-containing chemotherapy 1 (0.2%) patients due to drug hypersensitivity.

Monitor patients during and after infusion with VYLOY (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). If an anaphylactic reaction occurs, administration of VYLOY (zolbetuximab) 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 (zolbetuximab) 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 (zolbetuximab) 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 and closely monitor the patient for symptoms and signs of a hypersensitivity reaction. The infusion rate may be gradually increased as tolerated.

In the integrated safety analysis, all grade **infusion-related reactions (IRR)** occurred in the VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy arm at 3% (19/631) compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm at 1.1% (7/611). Severe (grade 3) IRRs occurred more frequently in the VYLOY (zolbetuximab) in

Important Safety Information, continued

combination with fluoropyrimidine- and platinum-containing chemotherapy arm [0.5% (3/631)] compared with the placebo in combination with fluoropyrimidine- and platinum-containing chemotherapy arm [0% (0/611)]. The median time to first onset of an IRR with VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy was 22 days. An IRR led to permanent discontinuation of VYLOY (zolbetuximab) in 3 (0.5%) patients and dose interruption in 9 (1.4%) patients. The infusion rate was reduced for VYLOY (zolbetuximab) or fluoropyrimidine- and platinum-containing chemotherapy in 2 (0.3%) patients due to an IRR.

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 (zolbetuximab) should be immediately and permanently discontinued and appropriate medical therapy instituted. For grade 2 IRRs, interrupt the VYLOY (zolbetuximab) 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 and closely monitor the patient for symptoms and signs of an IRR. The infusion rate may be gradually increased as tolerated.

In the integrated safety analysis, all grade **nausea and vomiting** occurred more frequently in the VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy arm (77% [486/631], 66.9% [422/631]) compared with the placebo in combination with fluoropyrimidine- and platinum-containing chemotherapy arm (58.6% [358/611], 36.2% [221/611]). Severe (grade 3) nausea in the VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy and placebo in combination with fluoropyrimidine- and platinum-containing chemotherapy arms occurred at 11.6% (73/631) and 4.6% (28/611), respectively. Severe (grade 3) vomiting in the VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy and placebo in combination with fluoropyrimidine- and platinum-containing chemotherapy arms occurred at 13.6% (86/631) and 4.6% (28/611), respectively. The median time to first onset of nausea or vomiting with VYLOY (zolbetuximab) in combination with fluoropyrimidine and platinum-containing chemotherapy was 1 day for both arms.

Nausea led to permanent discontinuation of VYLOY (zolbetuximab) in 21 (3.3%) patients and dose interruption in 161 (25.5%) patients. Vomiting led to permanent discontinuation of VYLOY (zolbetuximab) in 24 (3.8%) patients and dose interruption in 167 (26.5%) patients. The infusion rate was reduced for VYLOY (zolbetuximab) or fluoropyrimidine- and platinum-containing chemotherapy in 59 (9.4%) patients due to nausea and in 49 (7.8%) patients due to vomiting.

To prevent nausea and vomiting, pre-treatment with anti-emetics is recommended prior to each infusion of VYLOY (zolbetuximab). During and after infusion, patients should be monitored and managed using standard of care, including anti-emetics or fluid replacement, as clinically indicated. For grade 4 vomiting, permanently discontinue treatment with VYLOY (zolbetuximab). For grade 2 or 3 nausea or vomiting, interrupt the VYLOY (zolbetuximab) infusion until grade ≤1, then resume at a reduced infusion rate for the remaining infusion. For the next infusion, closely monitor the patient for symptoms and signs of nausea or vomiting. The infusion rate may be gradually increased as tolerated.

Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of VYLOY (zolbetuximab) in pregnant women. No adverse effects were observed in an animal reproductive and developmental study with intravenous administration of VYLOY (zolbetuximab) to pregnant mice during organogenesis. Based on area under the curve, the doses administered in this study were up to approximately 1.8 times higher than human exposure at the recommended therapeutic dose of 600 mg/m^2. VYLOY (zolbetuximab) should only be given to a pregnant woman if the benefit outweighs the potential risk.

VYLOY™
zolbetuximab
for infusion 100mg vial

Important Safety Information, continued

Breastfeeding
There are no data on the presence of VYLOY (zolbetuximab) in human milk, the effects on the breastfed child or the effects on milk production. Because many drugs, including 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 (zolbetuximab).

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

Interaction with other medicinal products and other forms of interaction
No *in vitro* or *in vivo* drug–drug interaction or transporter studies have been conducted.

Effects on ability to drive and use machines
No studies with VYLOY (zolbetuximab) and the effects on the ability to drive or use machines have been performed. Based on reported adverse reactions, VYLOY (zolbetuximab) has no or negligible influence on the ability to drive and use machines.

References:

1. VYLOY (zolbetuximab) Summary of Product Characteristics. **2.** Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): A multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2023;401(10389):1655–1668. **3.** Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: The randomized, phase 3 GLOW trial. *Nat Med* 2023;29(8):2133–2141. **4.** Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): A multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2023;401(10389):1655–1668. Supplement.

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