DRUG NAME: Zolbetuximab

SYNONYM(S)[1]: IMAB 362, GC 182, claudiximab, zolbetuximab-clzb

COMMON TRADE NAME(S): VYLOY®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Zolbetuximab is a chimeric murine/human IgG monoclonal antibody that targets Claudin18 isoform 2 (CLDN18.2). CLDN 18.2 is a tight junction protein mainly found in normal gastric mucosal cells where it remains buried within tight junctions. However, during malignant transformation, CLDN18.2 become exposed on the cell surface due to the loss of cell polarity. By binding to CLDN 18.2, zolbetuximab activates the complement cascade (complement-dependent cytotoxicity) and immune effector cells (antibody-dependent cellular cytotoxicity), resulting in cell lysis of CLDN18.2-positive cells. Studies have shown that combining zolbetuximab with chemotherapy enhances its antitumour activity by sensitizing tumour cells to zolbetuximab.[2-4]

PHARMACOKINETICS:

Distribution	primarily limited to vascular space	
	cross blood brain barrier?	no information found
	volume of distribution	5.5 L at steady state
	plasma protein binding	no information found
Metabolism	expected to be catabolized into small peptides and amino acids	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	clearance decreases over time[5]	
	urine	no information found
	feces	no information found
	terminal half life	17 days (range 9-45 days)
	clearance	9.95 mL/day
Sex	no clinically significant differences	
Elderly	no clinically significant differences	
Ethnicity	no clinically significant differences	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

Gastric cancer*

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:

- severe ***nausea and vomiting*** are reported with zolbetuximab despite the use of antiemetic prophylaxis[2,4,6]; premedication with antiemetics is recommended prior to each infusion[3]

Carcinogenicity: No studies have been conducted.[3]

Mutagenicity: No studies have been conducted.[3]

Fertility: No studies have been conducted.[3]

Pregnancy: In animal studies, no embryo-fetal toxicity was observed when zolbetuximab was administered during the period of organogenesis at exposures up to 1.8 times higher than those seen following human clinical dosing. Zolbetuximab crosses the placental barrier. Reported fetal serum concentrations of zolbetuximab were higher on gestation day 18 than the maternal serum concentrations in the test subjects on day 16.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Human IgG is known to be excreted in human milk. Breastfeeding should be avoided during treatment and for 8 months after the final dose of zolbetuximab.[3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7,8] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group. **Incidence data from combination regimens with chemotherapy is indicated with an asterisk (*).**[2-4]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (11-20%, severe 2-10%)
	neutropenia (7%)
gastrointestinal	*emetogenic potential:* high[10,11]
	abdominal pain (13-40%, severe 4-10%)
	constipation (17-26%)
	diarrhea (10-26%, severe 6%)
	dyspepsia (10%)
	nausea (63%, severe 7-15%); see paragraph following **Side Effects** table
	salivary hypersecretion (1-10%)*[2,3]; has been reported as an infusion-related reaction
	vomiting (37-57%, severe 7-22%); see paragraph following **Side Effects** table
general disorders and administration site conditions	*extravasation hazard:* none[12]
	asthenia (22-27%, severe 3-7%)
	fatigue (7-43%, severe 4%)
	peripheral edema (22%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pyrexia (20%, severe 3%)
immune system	***hypersensitivity*** (18-36%, severe 1-5%)[3,9]; see paragraph following **Side Effects** table
injury, poisoning, and procedural complications	***infusion-related reaction*** (3%, severe <1%)[3]; see paragraph following **Side Effects** table
investigations	weight loss (3-15%)
	glucose decrease (6-10%, severe <1%)*[3]
	glucose increase (≥15%, severe 2%)*[9]
metabolism and nutrition	***appetite decrease*** (23-30%, severe 4%)
	hypoalbuminemia (8-9%, severe 3%)*[3]
	hypocalcemia (8%, severe 2%)*[3]
	hypokalemia (7%, severe 5%)*[3]
	hyponatremia (8%, severe 2%)*[3]
musculoskeletal and connective tissue	back pain (10%)
	myalgia (3%)
psychiatric	insomnia/sleep disorder (13%)
nervous system	dizziness (5%)
	neuropathy, peripheral sensory (3%)
	paresthesia (3%)
respiratory, thoracic, and mediastinal	cough (10%)
	dyspnea (15%, severe 11%)
	pleural effusion (11%, severe 2%)
skin and subcutaneous tissue	pruritus (3%)
vascular	hypertension (13%, severe 10%)

Adapted from standard reference[13,14] unless specified otherwise.

Severe ***nausea and vomiting*** are reported with zolbetuximab despite the use of antiemetic prophylaxis.[2,4,6] Symptoms are most common with the first two infusions of zolbetuximab, but occur with reduced incidence in subsequent cycles.[2,3] During the first infusion of zolbetuximab, nausea and/or vomiting typically occur within 1 hour, with a median time to onset reported as 48 to 57 minutes.[6] To prevent nausea and vomiting, premedication with antiemetics is recommended prior to each infusion.[3] Histopathologic studies show that vomiting is associated with gastric mucosal tissue damage induced by zolbetuximab.[15] Patients without prior gastrectomy are more likely to experience nausea and vomiting.[14] The incidence of vomiting is also higher when zolbetuximab is given in combination regimens with chemotherapy compared to zolbetuximab alone.[3,13,14] Zolbetuximab should not be initiated in patients experiencing nausea or vomiting prior to treatment unless their symptoms have resolved to grade 1 or less.[2,3] In patients with an intact stomach, consider starting a H2 receptor antagonist or proton pump inhibitor prior to zolbetuximab to protect gastric mucosa and to help prevent dyspepsia, which can mimic nausea.[16] For grade 2 or 3 events of nausea and vomiting, hold infusion until symptoms improve to grade 1 or less, then resume infusion at a reduced rate. Permanently discontinue zolbetuximab for grade 4 vomiting.[3]

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Infusion-related reactions (IRRs) have been reported with zolbetuximab. Signs and symptoms include nausea, vomiting, abdominal pain, salivary hypersecretion, pyrexia, chest discomfort, chills, back pain, cough, and hypertension. ***Hypersensitivity reactions***, including anaphylactic reactions, are also reported. Monitor patients during and after infusion for signs of anaphylaxis such as urticaria, persistent cough, wheezing, throat tightness, or change in voice. To minimize reactions, start each infusion at the recommended initial rate and increase the rate as tolerated. For patients who have experienced grade 2 IRRs or hypersensitivity reactions, premedication with antihistamines is recommended prior to subsequent infusions. Permanently discontinue zolbetuximab in the event of grade 3 or 4 reactions, or if anaphylaxis is suspected.[3] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

INTERACTIONS:

No known interactions. Zolbetuximab is not a cytokine modulator and has no known effects on cytochrome P450 or drug transporters.[3]

SUPPLY AND STORAGE:

***Injection*:** Astellas Pharma Canada Inc. supplies zolbetuximab as 100 mg single-dose (preservative free) vials of lyophilized powder. Refrigerate. Protect from light. Do not shake.[3]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

<table>
<tr><td>Subcutaneous</td><td>no information found</td></tr>
<tr><td>Intramuscular</td><td>no information found</td></tr>
<tr><td>Direct intravenous</td><td>do not use</td></tr>
<tr><td rowspan="3">Intermittent infusion[3]</td><td>• loading dose (800 mg/m^2): over 3-6 h
• maintenance doses (400-600 mg/m^2): over 2-5 h</td></tr>
<tr><td>administer with 0.2 micron in-line filter</td></tr>
<tr><td>In the absence of other guidelines, the following incremental infusion rate may be used for each infusion:
<table>
<tr><th colspan="2">Dose</th><th>Initial infusion rate* (for first 30-60 min)</th><th>Subsequent infusion rate</th></tr>
<tr><td>Loading dose</td><td>800 mg/m^2</td><td>75 mg/m^2/h</td><td>150-300 mg/m^2/h</td></tr>
<tr><td rowspan="2">Maintenance doses</td><td>600 mg/m^2</td><td>75 mg/m^2/h</td><td>150-300 mg/m^2/h</td></tr>
<tr><td>400 mg/m^2</td><td>50 mg/m^2/h</td><td>100-200 mg/m^2/h</td></tr>
</table>
*escalate to subsequent infusion rate in the absence of infusion reactions in first 30-60 min</td></tr>
</table>

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BC Cancer administration guideline noted in ***bold***, ***italics***

Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	3 weeks[2-4]	**Loading dose**: 800 mg/m^2 IV for one dose on day 1 of first cycle (total dose per cycle 800 mg/m^2) **Maintenance dose**: 600 mg/m^2 IV for one dose on day 1 of each subsequent cycle (total dose per cycle 600 mg/m^2)
	2 weeks[3]	**Loading dose**: 800 mg/m^2 IV for one dose on day 1 of first cycle (total dose per cycle 800 mg/m^2) **Maintenance dose**: 400 mg/m^2 IV for one dose on day 1 of each subsequent cycle (total dose per cycle 400 mg/m^2) Dose reductions are not recommended.[3]
Concurrent radiation:	no information found	
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required[3] CrCl <30 mL/min: no information found calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04	
Dosage in hepatic failure:	mild impairment (total bilirubin ≤1.5 x ULN and any AST): no adjustment required[3] moderate to severe impairment (total bilirubin >1.5 x ULN and any AST): no information found	
Dosage in dialysis:	no information found	

Children: safety and efficacy not established

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