DRUG NAME: Gemtuzumab ozogamicin

SYNONYM(S): CMA-676[1]

COMMON TRADE NAME(S): MYLOTARG®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of a humanized IgG4 kappa-monoclonal antibody (gemtuzumab) linked to a small molecule cytotoxic agent (N-acetyl-gamma-calicheamicin dimethylhydrazide). The ADC recognizes and binds human CD33-expressing tumour cells. Following binding, the resulting ADC-CD33 complex is internalized and calicheamicin is released intracellularly. Calicheamicin induces double-stranded DNA breaks and subsequent cell cycle arrest and apoptosis. Gemtuzumab ozogamicin is cell cycle phase-nonspecific. Gemtuzumab ozogamicin is an immunosuppressive agent.[1-4]

PHARMACOKINETICS:

Distribution	calicheamicin is a substrate of P-glycoprotein	
	cross blood brain barrier?	no information found
	volume of distribution	25 L
	plasma protein binding	97% (calicheamicin)
Metabolism	primarily by non-enzymatic reduction (calicheamicin)	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily biliary excretion[5]	
	urine	no information found
	feces	no information found
	terminal half life	160 h
	clearance	0.3 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Leukemia, acute myeloid

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- ***infusion-related reactions,*** including anaphylaxis, are reported; premedication with a corticosteroid, antihistamine, and acetaminophen is recommended for all patients prior to each dose of gemtuzumab ozogamicin[2,3]

Developed: 1 September 2020
Revised: 1 February 2021

- ***tumour lysis syndrome,*** including fatal events complicated by acute renal failure, have been reported; consider leukoreduction to below 30,000/mm^3 prior to initiating gemtuzumab ozogamicin[2,3]
- ***QT prolongation*** has been reported; monitor ECG and electrolytes in patients with known risk factors[2,3]
- ***veno-occlusive disease/sinusoidal obstruction syndrome*** has been reported and is sometimes fatal; patients with moderate or severe hepatic impairment are at increased risk[2,3]

Carcinogenicity: In animal studies, preneoplastic lesions (minimal to slight oval cell hyperplasia) were observed in the liver at exposures higher than those seen following human clinical exposure.[2,3]

Mutagenicity: Mutagenic in Ames test. Gemtuzumab ozogamicin is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2,3]

Fertility: In animal studies, the number of corpora lutea and implants were reduced in female subjects. Dose-related decreases in the number of live embryos were observed at lower exposures than those seen following human clinical exposure. Atrophy in the ovary, oviduct, uterus, and cervix was observed at higher exposures than those seen following human clinical exposure. Male subjects experienced decreased size and weight of the testes and epididymides, lower spermatogonia and spermocytes, decreased testicular spermatids and epididymal sperm, vacuolation of the nucleus in spermatids, and appearance of giant cells.[2,3]

Pregnancy: In animal studies, embryo-fetal effects were observed in the presence of maternal toxicity. Increased embryolethality and fetal morphological abnormalities (e.g., lower fetal body weight, reduced skeletal ossification, fetal wavy ribs) were observed. Embryo-fetal effects were observed at lower exposures than those seen following human clinical exposure. Female patients of reproductive potential should use effective contraception during treatment and for at least seven months after the last dose. Male patients with female partners of reproductive potential should also use effective contraception during treatment and for at least four months after the last dose.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for at least one month following the last dose.[2,3]

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.[6] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (27%, severe 24%)
	febrile neutropenia (19%, severe 12%)
	leukopenia (27%, severe 27%)
	lymphopenia (4%, severe 3%)
	neutropenia (30%, severe 29%)
	pancytopenia (5%, severe 4%)
	thrombocytopenia (49%, severe 48%)
cardiac	tachycardia (13%, severe 2-4%)
gastrointestinal	*emetogenic potential:* moderate[7]

Developed: 1 September 2020
Revised: 1 February 2021

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	abdominal pain (33%, severe 7%)
	ascites (3%, severe <1%)
	constipation (21-25%, severe 5%)
	diarrhea (34%, severe 2-15%)
	dyspepsia (9%, severe 1%)
	esophagitis (2%, severe 1%)
	nausea (71%, severe 39%)
	stomatitis (21-36%, severe 4-12%)
	vomiting (61%, severe 34%)
general disorders and administration site conditions	*extravasation hazard:* none[8]; some cases of extravasation and injection site reactions or inflammation have been reported[9]
	chills (68%, severe 17%)
	edema (21%, severe 3%)
	fatigue (41%, severe 11%)
	multi-organ failure (2%, severe 1%); fatal events reported
	pyrexia (79-83%, severe 16-52%)
hepatobiliary	Budd-Chiari syndrome (severe <1%)
	gamma-glutamyltransferase increase (2%, severe 1%)
	hepatic failure (<1%, severe <1%); fatal events reported
	hepatomegaly (3%, severe 1%)
	hyperbilirubinemia (13%, severe 11%)
	jaundice (2%, severe 1%)
	transaminases increase (16-40%, severe 19%)
	veno-occlusive liver disease (3%, severe 1%); see paragraph following **Side Effects** table
infections and infestations	***infection*** (42-68%; severe 33-35%); see paragraph following **Side Effects** table
	sepsis (severe 32%)[3]
injury, poisoning, and procedural complications	***infusion-related reaction*** (8%, severe 4%); see paragraph following **Side Effects** table
investigations	alkaline phosphatase increase (9%, severe 6%)
	LDH increase (17%, severe 7%)
metabolism and nutrition	appetite decrease (27%, severe 6%)
	hyperglycemia (11%, severe 7%)
	tumour lysis syndrome (3%, severe 2%)
nervous system	headache (19-38%, severe 2-12%)

Developed: 1 September 2020
Revised: 1 February 2021

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
respiratory, thoracic and mediastinal	dyspnea (27%, severe 13%)
skin and subcutaneous tissue	erythema (9%, severe 2%)
	pruritis (5%, severe >1%)
	rash (16-20%, severe 6-11%)
vascular	***hemorrhage/bleeding*** (23-67%, severe 7-24%); see paragraph following **Side Effects** table
	hypertension (17%, severe 11%)
	hypotension (20%, severe 15%)

Adapted from standard reference[3,10] unless specified otherwise.

Hepatotoxicity has been reported, including life-threatening or fatal events of hepatic failure and hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS). Patients at greater risk for developing VOD/SOS include those receiving gemtuzumab ozogocamin monotherapy, patients needing hematopoietic stem cell transplant (HSCT), and patients with moderate or severe hepatic impairment. Monitor all patients for elevated transaminases, total bilirubin, and alkaline phosphatase, plus signs of hepatomegaly, rapid weight gain, and ascites. More frequent monitoring is indicated for patients with abnormal liver tests and patients who proceed to HSCT. Dose reduction and treatment interruption or discontinuation may be required to manage elevated liver panel values. Discontinue gemtuzumab ozogamicin if VOD/SOS develops.[2,3,10]

Infusion-related reactions, including anaphylaxis, have been reported and may be life-threatening. Fever, chills, hypotension, tachycardia, and respiratory symptoms may occur during the infusion or within 24 hours following the infusion. Premedication with a corticosteroid, antihistamine, and acetaminophen is recommended prior to each dose of gemtuzumab ozogamicin.[2,3,10] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents*.**

Myelosuppression is reported. Life-threatening ***infection*** and fatal events associated with myelosuppresson have been reported, including fungal lung infections (e.g., pulmonary mycosis and Pneumocystis jirovecii), septic shock, neutropenic colitis, hemorrhagic cystisis, and interstitial pneumonia. Patients are also at risk for life-threatening ***bleeding/hemorrhagic events*** due to prolonged thrombocytopenia. Events such as cerebral hematoma and intracranial or subdural hemorrhage have been reported and may be fatal. Treatment interruption or permanent discontinuation of gemtuzumab ozogamicin may be required for severe or persistent myelosupression.[2,3]

INTERACTIONS: no known interactions[2-4]

SUPPLY AND STORAGE:

***Injection*:** Pfizer Canada ULC supplies gemtuzumab ozogamicin as 4.5 mg single-use vials of lyophilized powder. Refrigerate. Protect from light in original packaging.[2]

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

Developed: 1 September 2020
Revised: 1 February 2021

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information:

- Gemtuzumab ozogamicin is light sensitive. ***Protect from light*** during ***reconstitution, dilution,*** and ***administration***. The infusion line does not need to be protected from light unless administration of the drug cannot be completed within two hours of hanging the drug.[2,3,9]
- To reduce the potential for drug adsorption, ***doses less than 3.9 mg*** should be prepared in a ***syringe*** for ***administration*** instead of a minibag. Note: Reconstituted gemtuzumab ozogamicin must be further diluted with normal saline to provide a final concentration of 0.075-0.234 mg/mL for administration, even when prepared as a syringe (e.g., doses of 1.89 mg to <3.9 mg may be diluted to a final volume of 25 mL in a syringe.)[2,11,12]

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use[2]
Intermittent infusion	***over 2 hours; administer using 0.2 micron inline filter***[2,3,13]
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. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

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

Intravenous:	Cycle Length: n/a[1-3,10,13]:	***induction***: ***3 mg/m^2 IV for one dose on days 1, 4, and 7*** OR on days 3, 6, and 9 ***(max dose = 4.5 mg)*** (total dose per induction 9 mg/m^2) ***consolidation***: ***3 mg/m^2 IV for one dose on day 1 (max dose = 4.5 mg)*** (total dose per cycle 3 mg/m^2)

Developed: 1 September 2020
Revised: 1 February 2021

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

Cycle Length:
n/a[1,3]: induction:
6 mg/m^2 IV for one dose on day 1, followed by 3 mg/m^2 IV for one dose on day 8 (no maximum dose)
(total dose per induction 9 mg/m^2)

consolidation:
2 mg/m^2 IV for one dose on day 1 every 4 weeks (no maximum dose)
(total dose per cycle 2 mg/m^2)

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure[2,3]:
CrCl ≥30 mL/min: no adjustment required
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure[2,3]:
bilirubin ≤2 x ULN and AST/ALT ≤2.5 x ULN: no adjustment required
bilirubin >2 x ULN and AST/ALT >2.5 x ULN: no information found; use is not recommended in patients with clinically significant liver disease such as cirrhosis or active viral hepatitis[6]

Dosage in dialysis: no information found

Children:

Intravenous:
Cycle Length:
n/a[1,3]: 3 mg/m^2 IV for one dose on days 1, 4, and 7 (max dose = 4.5 mg)
(total dose per course 9 mg/m^2)

REFERENCES:

1. Lexi-Drugs® - Lexicomp Online (database on the Internet). Gemtuzumab ozogamicin. Wolters Kluwer Clinical Drug Information Inc., 21 April 2020. Available at: http://online.lexi.com. Accessed 8 June 2020.
2. Pfizer Canada ULC. MYLOTARG® product monograph. Kirkland, Quebec; 28 November 2019.
3. Pfizer Inc. MYLOTARG® full prescribing information. Philadelphia, PA, USA; April 2020.
4. AHFS Drug Information® - Lexicomp Online (database on the Internet). Gemtuzumab ozogamicin. Wolters Kluwer Clinical Drug Information Inc., 4 March 2020. Available at: http://online.lexi.com. Accessed 8 June 2020.

Developed: 1 September 2020
Revised: 1 February 2021

5. Bross PF, Beitz J, Chen G, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clinical Cancer Research 2001;7:1490-1496.
6. David Sanford MD. BC Cancer Leukemia and Bone Marrow Transplant Tumour Group. Personal communication. 30 July 2020.
7. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 Dec 2018.
8. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; January 2016.
9. Sharon Keane. Pfizer Canada Medical Information. Personal communication. 7July 2020.
10. Pfizer Europe MA EEIG. MYLOTARG® product monograph (EU). Bruxelles, Belgium; 19 April 2018.
11. Pfizer Inc. MYLOTARG® dosing and adminstration guide. Philadelphia, PA, USA; March 2018.
12. Pfizer Canada Medical Information. Personal communication. 10 August 2020.
13. BC Cancer Leukemia and Bone Marrow Transplant Tumour Group. (ULKGEMOZ) BC Cancer Protocol Summary for Treatment of Acute Myeloid Leukemia Using Gemtuzumab Ozogamicin with Induction and Consolidation Chemotherapy. Vancouver, British Columbia: BC Cancer; 1 February 2021.

Developed: 1 September 2020
Revised: 1 February 2021