Drug Monograph

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A - Drug Name

gemtuzumab ozogamicin

COMMON TRADE NAME(S): Mylotarg®

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B - Mechanism of Action and Pharmacokinetics

Gemtuzumab ozogamicin is a CD33-directed monoclonal antibody-drug conjugate (ADC). The antibody portion that recognizes the human CD33 antigen is covalently attached to a cytotoxic calicheamicin derivative, via a linker. The anticancer activity of gemtuzumab ozogamicin is due to the binding of the ADC to CD33-expressing tumor cells, followed by internalization of the ADC-CD33 complex. Following internalization, the calicheamicin derivative is released intracellularly and binds to DNA resulting in double strand breaks, inducing cell cycle arrest and apoptosis.

Distribution	PPB	N-acetyl gamma calicheamicin dimethyl hydrazide: ~97% to human plasma proteins
Metabolism	N-acetyl gamma calicheamicin dimethyl hydrazide is extensively metabolized, primarily through nonenzymatic reduction of the disulfide moiety.	
	Active metabolites	Yes, but activity of the metabolites is expected to be significantly attenuated
Elimination	Half-life	Based on a 3 mg/m^2 dose: Antibody portion: ~160 hours
	Clearance	Antibody portion: 3 L/hour (after first dose); 0.3 L/hour. (after second dose)

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C - Indications and Status

Health Canada Approvals:

- Acute myeloid leukemia (AML)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low

The following table lists adverse effects that occurred in ≥ 1% of patients, in the phase III study with previously untreated de novo AML who received gemtuzumab ozogamicin as combination therapy. Incidences marked with "∞" were reported from monotherapy trials in newly diagnosed or relapsed/refractory AML. The table also includes severe or life-threatening adverse effects from post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Acute coronary syndrome (rare)	E
	Tachycardia (2%) (severe)∞	E
Dermatological	Rash (16%) ∞	E
Gastrointestinal	Constipation (21%) ∞	E
	Diarrhea (2%) (severe)∞	E
	Mucositis (2%)	E
	Nausea, vomiting (21%) ∞	I
General	Fatigue (46%) (12% severe)∞	E
Hematological	Febrile neutropenia (18%) ∞	E
	Hemorrhage (90%) (e.g., upper or lower GI, subcut, pulmonary, epistaxis, hematuria, CNS and others) (23% ≥ grade 3)	E
	Myelosuppression (19%) (prolonged thrombocytopenia¥; 3% prolonged neutropenia†) (during induction)	E
Hepatobiliary	Cholecystitis (rare)	E

	Hepatotoxicity (13%) (≥ grade 3)	E
	Veno-occlusive disease (5%) (including sinusoidal obstruction syndrome)	E
Infection	Infection (78%) (≥ grade 3) (including fungal infections)	E
Metabolic / Endocrine	Hyperuricemia (3%)	I E
	Tumor lysis syndrome (2%)	I E
Nervous System	Headache (19%) ∞	E
Renal	Renal failure (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

¥Platelets < 50 × 10^9/L, lasting past cycle Day 42 in the absence of active leukemia.

†Neutrophils < 0.5 × 10^9/L, lasting past cycle Day 42 in the absence of active leukemia.

The most common side effects for gemtuzumab ozogamicin include hemorrhage, infection, fatigue, constipation, nausea, vomiting, headache, myelosuppression, febrile neutropenia, rash and hepatotoxicity.

Hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic **veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS)** events, was reported with the use of gemtuzumab ozogamicin as a single agent, and as part of a combination chemotherapy regimen, in patients without a history of liver disease or hematopoietic stem cell transplant (HSCT). In the combination therapy study, the median time to VOD onset was 9 days (range:2 to 298 days). Adults who receive gemtuzumab ozogamicin as monotherapy, either before or after an HSCT, and those with moderate to severe baseline hepatic impairment, appear to be at increased risk for VOD/SOS.

Gemtuzumab ozogamicin is **myelosuppressive**; neutropenia, thrombocytopenia, anemia, leukopenia, febrile neutropenia, lymphopenia, and pancytopenia, some of which were life-threatening or fatal, have been reported. Prolonged thrombocytopenia (>42 days post dose) has also been reported. Complications associated with neutropenia and thrombocytopenia may include infections and bleeding/hemorrhagic events. The median times for platelet recovery to 50 x 10^9/L and 100 x 10^9/L for the induction phase ranged from 34-35 days and platelet recovery for Consolidation 1 and 2 phases ranged from 32-43 days. The median times for neutrophil recovery to ANC of 0.5 x 10^9/L and 1 x 10^9/L for the induction phase was 25 days and neutrophil recovery for Consolidation 1 and 2 phases ranged from 21-27 days.

Life-threatening or fatal **infections** and **bleeding/hemorrhagic** events have been reported. Fatal

bleeding events included CNS hematomas.

Life-threatening or fatal **infusion-related reactions** which may occur within 24 hours of gemtuzumab ozogamicin infusions, have been reported. Signs and symptoms of infusion related reactions may include fever and chills, and less frequently hypotension, tachycardia, and respiratory symptoms.

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E - Dosing

Refer to protocol by which patient is being treated.

Pre-medications (prophylaxis for infusion reaction):

Give 1 hour prior to gemtuzumab ozogamicin:

- a corticosteroid (e.g., 1 mg/kg methylprednisolone or equivalent)
- an antihistamine PO or IV (e.g., diphenhydramine 50 mg), and
- acetaminophen PO (e.g., acetaminophen 650 mg)

To prevent tumour lysis syndrome, initiate hydration and antihyperuricemic agent (or other agents for hyperuricemia) as necessary.

Cytoreduction is recommended prior to gemtuzumab ozogamicin administration if leukocyte count >30 x 10^9/L:

- Reduce peripheral WBC count 48 hours prior to administration of gemtuzumab ozogamicin according to institutional guidelines..

Adults:

Combination therapy*:*

Note: A treatment course consists of 1 induction cycle and 2 consolidation cycles.

Induction:

Intravenous: 3 mg/m² (up to a maximum dose of 4.5 mg) Days 1, 4, and 7

(in combination with daunorubicin and cytarabine)

If cytarabine is used for leukoreduction with or without hydroxyurea, refer to the modified induction schedule in the product monograph.

For patients requiring a second induction cycle, do NOT administer gemtuzumab ozogamicin during the second induction cycle.

Consolidation (2 cycles):

Intravenous: 3 mg/m² (up to a maximum dose of 4.5 mg) Day 1

(in combination with cytarabine*, OR daunorubicin and cytarabine)

*based on NDFP form.

See CYTADAUN+GEMT for daunorubicin and cytarabine dosing or CYTA(HD)+GEMT for cytarabine dosing.

Dosage with Toxicity:

Hematologic Toxicities

Toxicity	Recommended Action
Persistent thrombocytopenia	If platelet count does not recover to ≥100 x 10^9/L within 14 days following the anticipated start date of the consolidation cycle*: • Discontinue • Do not administer during the consolidation cycles
Persistent neutropenia	If neutrophil count does not recover to ≥0.5 x 10^9/L within 14 days following the anticipated start date of the consolidation cycle*: • Discontinue • Do not administer in the consolidation cycles

*14 days after hematologic recovery following previous cycle

Non-Hematologic Toxicities

Toxicity	Recommended Action	
VOD/SOS	Discontinue	
Total bilirubin > 2 × ULN, or AST and/or ALT > 2.5 × ULN	Hold until recovery of: • Total bilirubin to ≤2 × ULN AND • AST and ALT to ≤2.5 × ULN prior to each dose Omit if delayed >2 days between sequential infusions	
Infusion-related reactions	Mild to moderate	Hold and initiate appropriate supportive care measures. With symptom resolution, consider resuming at ≤50% of the rate at which the reaction occurred. If symptoms recur, repeat procedure above.
	Severe or life-threatening	Discontinue
Other severe or life threatening nonhematologic toxicities	Hold until recovery to a severity of no more than mild. Omit if delayed >2 days between sequential infusions.	

Dosage with Hepatic Impairment:

Hepatic Impairment	Total bilirubin		AST	Gemtuzumab Ozogamicin Dose
Mild	≤ ULN	and	>ULN	No dose adjustment required
	>1 to 1.5 x ULN		Any	
Moderate	>1.5 to 3 x ULN		Any	No data available

Severe	>3 x ULN		Any	

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Gemtuzumab Ozogamicin Dose
≥ 30	No dose adjustment required
< 30	No data available

Dosage in the elderly:

No dose adjustment is required as no overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

Children:

Safety and efficacy of gemtuzumab ozogamicin have not been established.

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F - Administration Guidelines

- Gemtuzumab ozogamicin is light sensitive; **protect from light** during reconstitution, dilution and administration.
- Protect the IV bag/syringe from light using a light-blocking cover during infusion. The infusion line does not need to be protected from light.
- Prior to reconstitution, allow gemtuzumab ozogamicin vials to reach room temperature (up to 30°C) for approximately 5 minutes.
- Do not shake during reconstitution or dilution, gently swirl the vial or invert container to mix the solution.
- Gemtuzumab ozogamicin vials are filled with 5 mg of drug product with a 0.5 mL overfill.

- Dilute dose in 0.9% sodium chloride to a concentration between 0.075 mg/mL to 0.234 mg/mL:
    - To reduce the potential for drug adsorption, doses <3.9 mg must be diluted in a syringe and administered IV over 2 hours.
    - Doses greater ≥3.9 mg are to be diluted in a syringe or an IV infusion bag and administered IV over 2 hours.
- Do not administer as an IV push or bolus.
- Do not mix gemtuzumab ozogamicin with, or administer as an infusion with, other drugs.
- Use PVC bags with DEHP, ethylene vinyl acetate (EVA) or polyolefin (polypropylene and/or polyethylene) and an in-line, low protein-binding 0.2 micron polyethersulphone (PES) filter for IV infusions.
- For doses administered by syringe, use small bore infusion lines (microbore) with an in-line, low protein-binding 0.2 micron polyethersulphone (PES) filter.
- Infuse the diluted solution using an infusion set made of polyvinyl chloride (PVC) with DEHP, PVC non-DEHP, polyethylene, or polyurethane.
- Flush the IV line after each dose with 0.9% sodium chloride.
- Monitor vital signs (pulse, blood pressure, and temperature) frequently during infusion and for at least 1 hour after the end of the infusion or until signs and symptoms of infusion-related-reactions completely resolve.
- Refrigerate unopened vials (2^{o}C to 8^{o}C); do not freeze and protect from light

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components.

Other Warnings/Precautions:

- Patients who have a history of or predisposition for QTc prolongation, who are taking medicinal products that are known to prolong QT interval and have electrolyte disturbances may be at increased risk for cardiac complications.
- Patients should use caution when driving or using machinery as fatigue, has been reported with treatment.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Yes
- Clastogenicity: Documented in animals
- Embryotoxicity: Probable
  Gemtuzumab ozogamicin is not recommended for use in pregnancy. 2 methods of effective contraception should be used by both sexes during treatment, and for at least **7 months** after the last dose in women and at least **4 months** after the last dose in men.
- Excretion into breast milk: Unknown
  Due to the potential for adverse reactions in the breastfed infant, breast-feeding is not recommended during treatment and for at least **1 month** after the final dose.
- Fertility effects: Documented in animals

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H - Interactions

N-acetyl gamma calicheamicin dimethyl hydrazide is primarily metabolized via nonenzymatic reduction. Therefore, coadministration of gemtuzumab ozogamicin with inhibitors or inducers of cytochrome P450 (CYP) or uridine diphosphate glucuronosyltransferase (UGT) drug metabolizing enzymes are unlikely to alter the exposure to the calicheamicin derivative.

At clinically relevant concentrations, N-acetyl gamma calicheamicin dimethyl hydrazide had a low potential to inhibit drug transporters (e.g., P-gp, BCRP, OAT1 and OAT3, OCT2, OATP1B1, OATP1B3, BSEP and MRP2).

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests (ALT, AST, total bilirubin, and ALP)	Baseline and prior to each dose; more frequently if clinically indicated, particularly if hepatotoxicity/VOD is suspected

	and/or in HSCT patients (including post-HSCT period).
CBC	Baseline, prior to and after each dose and ≥ 3 times/week until recovery from treatment-related toxicities.
Serum chemistries, including creatinine and electrolytes	Baseline, as clinically indicated and ≥ 3 times/week until recovery from treatment-related toxicities.
ECG	Baseline and as clinically indicated (in patients who are at risk or have a history of QT prolongation)
Clinical toxicity assessment for TLS, infusion related reactions, infection, bleeding/hemorrhage, cardiovascular, VOD/SOS, GI effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

High Cost Therapy Funding Program ()

- Gemtuzumab Ozogamicin (Inpatient) - Previously Untreated Acute Myeloid Leukemia

New Drug Funding Program (NDFP Website)

- Gemtuzumab Ozogamicin (Outpatient) - Previously Untreated Acute Myeloid Leukemia

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K - References

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Product Monograph: Mylotarg® (gemtuzumab ozogamicin), Wyeth LLC Pfizer Canada ULC, September 20, 2021.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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