Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

inotuzumab ozogamicin

COMMON TRADE NAME(S): Besponsa®

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B - Mechanism of Action and Pharmacokinetics

Inotuzumab ozogamicin is an antibody-drug conjugate, consisting of inotuzumab, an anti-CD22 IgG4 antibody linked to a cytotoxic component (N-acetyl-gamma-calicheamicin).

Distribution	Steady state concentration was achieved by cycle 4.	
	PPB	97%
Metabolism	The cytotoxic component is primarily metabolized through non-enzymatic reduction.	
Elimination	Half-life	12.3 days

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C - Indications and Status

Health Canada Approvals:

Monotherapy for the treatment of adults with relapsed or refractory CD22-positive* B-cell precursor

acute lymphoblastic leukemia (ALL)

(*determined by a validated assay)

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D - Adverse Effects

Emetogenic Potential: Low

The following adverse effects were from the phase III relapsed or refractory ALL trial and occurred in ≥ 1% of patients who received inotuzumab ozogamicin.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	QT interval prolonged (6%) (also PR prolongation)	E D
Gastrointestinal	Abdominal pain (23%)	E
	Anorexia (12%)	E
	Constipation (16%)	E
	Diarrhea (17%)	E
	Mucositis (13%)	E
	Nausea, vomiting (31%) (2% severe)	I
General	Fatigue (35%)	E
	Fever, chills (32%) (3% severe)	I
Hematological	Myelosuppression ± infection, bleeding (51%) (48% severe)	E
Hepatobiliary	↑ Amylase / lipase (9%) (4% severe)	E
	↑ LFTs (26%) (severe 10%)	E
	Veno-occlusive disease (VOD; 3-23%) or Sinusoidal Obstruction Syndrome (SOS)	E D
Hypersensitivity	Infusion related reaction (2%) (Grade 1-2)	I
Immune	Antibody response (3%)	E D
Metabolic / Endocrine	Tumor lysis syndrome (2%)	E
Nervous System	Headache (28%)	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)

The most common side effects for inotuzumab ozogamicin include myelosuppression ± infection, bleeding, ↑ LFTs, fatigue, ↑ amylase / lipase, fever/chills, nausea/vomiting, headache, abdominal pain and constipation.

Infusion-reaction reactions were ≤ grade 2 in severity. They generally occurred in cycle 1 shortly after the end of inotuzumab ozogamicin infusion.

Patients at risk of **tumour lysis syndrome** (TLS) should have appropriate prophylaxis and be monitored closely.

Inotuzumab ozogamicin is associated with **QT and PR prolongation.** Risk factors include: female gender, age ≥ 65 years, baseline QT/QTc prolongation, congenital long QT syndromes, family history of sudden cardiac death at < 50 years of age, cardiac disease, history of arrhythmias, electrolyte disturbances, acute neurologic events, autonomic neuropathy, or diabetes.

Bacterial, viral and fungal **infections** were reported, and may be severe.

Hepatotoxicity, including severe and fatal hepatic **Veno-occlusive disease (VOD)/ Sinusoidal obstruction syndrome (SOS)** were observed. VOD/SOS has occurred up to 56 days after the last dose, while time from hematopoietic stem cell transplant (HSCT) to VOD/SOS onset was 15 days (range: 3-57 days). Risk is increased with:

- prior VOD/SOS or have serious ongoing hepatic disease
- prior HSCT
- subsequent HSCT (especially conditioning with 2 alkylating agents and last total bilirubin level ≥ ULN before follow-up HSCT)
- Increased age, history of liver disease and/or hepatitis before treatment, later salvage lines and a greater number of treatment cycles

Higher **post-HSCT non-relapse mortality** rate was observed in the inotuzumab arm (39% vs 23%), but more inotuzumab patients received HSCT (48% vs 22%). The most common causes of post-HSCT non-relapse mortality were VOD/SOS and infections.

Anti-inotuzumab ozogamicin antibodies were observed, but were not neutralizing and did not affect drug clearance after treatment. The impact of these antibodies on efficacy and safety are unknown.

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E - Dosing

Refer to protocol by which patient is being treated.

Hypokalemia, hypomagnesemia and hypocalcemia should be corrected before inotuzumab ozogamicin administration.

Patients at risk for tumour lysis syndrome should receive adequate hydration, prophylaxis and be monitored closely.

For patients with circulating lymphoblasts, cytoreduction is recommended prior to the first dose (to a peripheral blast count ≤ 10,000/mm^3) with a combination of hydroxyurea, steroids and/or vincristine.

Consider prophylactic anti-infectives.

Pre-medications (prophylaxis for infusion reaction):

- Corticosteroid, antipyretic, and antihistamine are recommended prior to each dose.

Adults:

Cycle 1 (q21 or 28 days†):

	Day 1	Day 8*	Day 15*
Dose for all patients (mg/m^2 IV)	0.8	0.5	0.5

† Cycle length may be extended up to 28 days for patients who achieve CR (complete remission) or CRi (complete remission with incomplete hematologic recovery), and/or to allow for recovery from toxicity.
* +/- 2 days (maintain at least 6 days between doses)

Subsequent cycles (q28 days):

For patients who achieved CR** or CRi^:

inotuzumab ozogamicin dose (mg/m^2 IV)		
Day 1	**Day 8***	**Day 15***
0.5	0.5	0.5

For patients who **did not** achieve CR** or CRi^:

inotuzumab ozogamicin dose (mg/m2 IV)		
Day 1	**Day 8***	**Day 15***
0.8	0.5	0.5

* +/- 2 days (maintain at least 6 days between doses)
** CR defined as < 5% blasts in bone marrow and absence of peripheral blood leukemic blasts, platelets **≥** 100 and ANC **≥** 1, and resolution of any extramedullary disease
^ CRi defined as < 5% blasts in bone marrow and absence of peripheral blood leukemic blasts, platelets **<** 100 and ANC **<** 1, and resolution of any extramedullary disease

Two cycles of treatment in total are recommended. Consider a total of 3 cycles for patients who do not achieve a CR or CRi and MRD negativity after 2 cycles.
For patients with CR or CRi and MRD negativity who are not proceeding with HSCT, may give up to 6 cycles.
Discontinue treatment if CR or CRi is **not** achieved within 3 cycles.

Dosage with Toxicity:

Hematologic toxicities:

Doses within a treatment cycle (e.g. days 8 and/or 15) do not need to be held due to neutropenia or thrombocytopenia.

If prior to inotuzumab ozogamicin treatment:	**Blood counts during cycle**	**Action (for next cycle)**
ANC ≥ 1 x 10^9/L	ANC decreases	Hold next cycle until ANC ≥ 1 x 10^9/L
Platelets ≥ 50 x 10^9/L*	Platelet count decreases	Hold next cycle until Platelets ≥ 50 x 10^9/L
ANC < 1 x 10^9/L and/or platelets* < 50 x 10^9/L	ANC or platelet count decreases	Hold next cycle until at least one of the following occurs: • ANC and platelet count recover to at least baseline for prior cycle • ANC ≥ 1 x 10^9/Land platelets ≥ 50 x 10^9/L

		• Stable or improved disease** and ANC and platelet decreases are due to underlying disease (not considered to be treatment-related)

*platelet count used for dosing should be independent of transfusion.
**based on most recent bone marrow assessment

Non-hematologic toxicities:

Dose interruptions within a cycle (e.g. days 8 and/or 15) are recommended for non-hematologic toxicities.

Non-Hematologic Toxicity	**Action**	**Dosing at Restart (if applicable)**			
		If dose held for ≤ 7 days (within a cycle)	**If dose held for ≥ 7 days**	**If dose held for ≥ 14 days**	**If dose held for > 28 days**
Bilirubin > 1.5 x ULN and AST/ALT > 2.5 x ULN	Hold until Bilirubin ≤ 1.5 x ULN and AST/ALT ≤ 2.5 x ULN (except in Gilbert's syndrome or hemolysis)	Hold next dose (maintain a minimum of 6 days between doses)	Omit next dose within the cycle	↓ total dose by 25% for the subsequent cycle. 2nd occurrence: Reduce the number of doses to 2 per cycle for subsequent cycles. 3rd occurrence: Discontinue	Discontinue
Other ≥ Grade 2 non-hematologic	Hold until ≤grade 1 or baseline before each dose				
VOD/SOS or other severe	Discontinue	Not applicable			

liver toxicity		

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a reduced infusion rate (ie. 50% at which IR occurred).	• Re-challenge with pre-medications and at a reduced infusion rate of 50% at which the IR occurred. • Consider adding montelukast ± acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Permanently discontinue (do not re-challenge).

Dosage with Hepatic Impairment:

Bilirubin		AST/ALT	Starting Dose
≤ 1.5 x ULN	and	≤ 2.5 x ULN	No adjustment required
> 1.5 x ULN	and	> 2.5 x ULN	Limited data; if not due to Gilbert's syndrome or hemolysis, do not treat.

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Starting Dose
≥ 30 (mild to moderate)	No adjustment required
15 to 29 (severe)	Limited data; use with caution
ESRD	No data

Dosage in the elderly:

No adjustment in starting dose is needed. No overall safety and efficacy differences between patients who were < 65 or ≥ 65 years of age. Increased age was associated with an increased risk of (VOD)/sinusoidal obstruction syndrome (SOS) after hematopoietic stem cell transplant.

Dosage based on gender:

No significant effects of gender on inotuzumab ozogamicin disposition

Dosage based on ethnicity:

No significant effects of ethnicity on inotuzumab ozogamicin disposition.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- Inotuzumab ozogamicin is light sensitive; **protect from light** during reconstitution, dilution and administration.
- Reconstitute inotuzumab ozogamicin using sterile water for injection according to instructions

in the product monograph.
- Further dilute the reconstituted drug in 0.9% sodium chloride solution, to a total volume of 50mL. Final concentration should be between 0.01 to 0.1 mg/mL.
- Do not shake the drug. Gently invert the drug container to mix.

- The diluted solution does not require filtration. If a filter is needed, polyethersulfone (PES), polyvinylidene fluoride (PVDF) or hydrophilic polysulfone (HPS)-based filters are recommended. Do not use filters made of nylon or mixed cellulose ester (MCE).
- Compatible with PVC, (DEHP or non-DEHP containing), polyolefin, or ethylene vinyl acetate (EVA) containers or infusion lines.

- The diluted solution may be refrigerated or stored at room temperature. (Refer to the product monograph for storage times.)
- If the diluted solution is refrigerated, it should remain at room temperature for about 1 hour before administration (protect from light).
- Infuse the diluted solution for 1 hour at a rate of 50 mL/hour.
- During administration, protect the infusion bag from light using an UV light-blocking cover (e.g. amber, dark brown or green bags or aluminum foil). The infusion line does not need to be protected from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Hypersensitivity to this drug or to any of its components

Other Warnings/Precautions:

- Not recommended for use in CD22-negative B-cell precursor ALL patients
- Use with caution in:
  - patients with a history of or risk factors for QTc prolongation or Torsade de pointes, who are taking medications known to prolong the QT interval, or
  - have electrolyte disturbances or pre-existing conduction system abnormalities, or
  - patients who have experienced prior VOD/SOS or patients with ongoing severe liver disease, or
  - patients who are older, have had a previous HSCT, in later lines of salvage and/or a previous history of liver disease and/or hepatitis
- Avoid using conditioning regimens containing 2 alkylating agents, to decrease risk of VOD/SOS after HSCT.
- Vaccination with live vaccines is not recommended for at least 2 weeks before starting

inotuzumab ozogamicin treatment, during treatment and until B-lymphocyte recovery after the final cycle.
- Inotuzumab ozogamicin has moderate influence on the ability to drive and use machines. Caution is recommended when performing these activities as patients may experience fatigue during treatment.

Pregnancy and Lactation:

- Genotoxicity: Yes
- Embryotoxicity: Yes
  Inotuzumab ozogamicin is not recommended for use in pregnancy. Female patients (and their male partners) should use adequate contraception during treatment, and for at least 8 months after the last dose. Male patients with partners of childbearing potential should use adequate contraception during treatment and for at least 5 months after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least 2 months after the last dose.
- Fertility effects:
  Fertility may be impaired

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H - Interactions

Concurrent use with cytoreductive drugs such as hydroxyurea, GCSF, and P-gp inhibitors had no apparent effect on inotuzumab.

Co-administration with inhibitors or inducers of CYP or UGT drug metabolizing enzymes are unlikely to alter exposure to the cytotoxic component (N-acetyl-gamma-calicheamicin dimethylhydrazide). Inotuzumab ozogamicin and its cytotoxic moiety have low potential to inhibit or induce certain CYP enzymes.

N-acetyl-gamma-calicheamicin dimethylhydrazide had a low potential to inhibit the activities of UGT drug metabolizing enzymes and drug transporters such as P-gp, BCRP, OAT1, OCT2, OAT3, OATP1B1 and OATP1B3.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine,	↑ risk of significant QT prolongation	Additive	If possible, discontinue other QT prolonging drugs and use alternatives that do not prolong QT. If unavoidable, monitor closely.

clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)			
Drugs that prolong PR interval (e.g. antiarrhythmics, beta blockers, non-dihydropyridine Ca channel blockers, digoxin, some HIV protease inhibitors, sphingosine-1 phosphate receptor modulators)	↑ risk of significant PR prolongation	Additive	Caution
Drugs that decrease electrolyte levels	↑ risk of arrhythmias		Avoid to the extent possible

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each dose
Liver function tests	Baseline, before and after each dose; more frequent if hepatotoxicity is suspected
Renal function tests	Baseline and before each cycle
Electrolytes	Baseline and as clinically indicated
Amylase and lipase	Baseline and as clinically indicated
ECGs	Baseline and as clinically indicated; more frequent in patients at risk of prolonged QT/PR

Infusion reactions	During and for at least 1 hour after the infusion
Clinical toxicity assessment for tumour lysis syndrome, infection, bleeding, fatigue, GI effects, VOD/SOS	At each visit
Post-HSCT patients	Monitor closely for hepatotoxicity and infection. Monitor liver function tests closely during the first month post-HSCT, then less frequently after

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

- Inotuzumab Ozogamicin (Inpatient) - Relapsed or Refractory Acute Lymphoblastic Leukemia

New Drug Funding Program (NDFP Website)

- Inotuzumab Ozogamicin (Outpatient) - Relapsed or Refractory Acute Lymphoblastic Leukemia

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K - References

Inotuzumab ozogamicin (Besponsa) Product Monograph. Pfizer Canada Inc., March 15, 2018.

Prescribing information: inotuzumab ozogamicin (Besponsa). Pfizer Inc. (US), March 2018.

July 2023 Updated NDFP and HCTFP forms

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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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