DRUG NAME: Inotuzumab ozogamicin

SYNONYM(S): CMC 544[1]

COMMON TRADE NAME(S): BESPONSA®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Inotuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of a humanized IgG4 kappa monoclonal antibody (inotuzumab) linked to a small molecule cytotoxic agent (N-acetyl-gamma-calicheamicin dimethylhydrazide). The ADC recognizes and binds human CD22-expressing tumour cells. Following binding, the resulting ADC-CD22 complex is internalized and calicheamicin is released intracellularly. Calicheamicin induces double-stranded DNA breaks and subsequent cell cycle arrest and apoptosis. Inotuzimab ozogamicin is cell cycle phase-nonspecific. Inotuzumab ozogamicin is an immunosuppressive agent.[2-5]

PHARMACOKINETICS:

Distribution	calicheamicin has 1.5 times greater distribution in tissue than blood; antibody-drug conjugate has 4.5 times greater distribution in blood than tissue[1]	
	cross blood brain barrier?	yes (in animal studies)[6]
	volume of distribution	12 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	linear and time-dependent clearance (2 compartment model)	
	urine	no information found
	feces	no information found
	terminal half life	12.3 days
	clearance	0.03 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

Leukemia, acute lymphoblastic*

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to inotuzumab ozogamicin or Chinese hamster ovary cell proteins[2]

Caution:

- ***infections*** commonly occur and are sometimes fatal; consider prophylactic anti-infectives and surveillance testing[2]

- ***infusion-related reactions*** are reported; premedication with a corticosteroid, antihistamine, and antipyretic is recommended for all patients prior to each dose of inotuzumab ozogamicin[2,7]
- ***QT interval prolongation*** has been reported; monitor ECG and electrolytes and use cautiously in patients with known risk factors[2]
- ***PR interval prolongation*** has been reported; caution in patients with pre-existing conduction abnormalities (e.g., AV block) or a history of rhythm disturbances (e.g., tachyarrhythmias)[2]
- immune response to ***vaccines*** may be diminished by inotuzumab ozogamicin[3]
- ***live attenuated vaccines*** should not be administered within the two weeks prior, during, or after treatment until B-cell recovery has occurred due to possible enhancement of vaccine adverse effects[2,3]
- ***tumour lysis syndrome*** has been reported, especially in patients with an initial high tumour burden; cytoreduction is advised prior to treatment initiation in patients with a high peripheral lymphoblast count[2]
- ***venoocclusive disease***/sinusoidal obstruction syndrome (VOD) is reported and is sometimes fatal; risk factors for VOD include use of conditioning regimens with two alkylating agents, having elevated bilirubin immediately before HSCT, and serious ongoing liver disease[2]

Special populations: Patients over 65 years of age are at greater risk of developing venoocclusive disease/sinusoidal obstruction syndrome post-hematopoietic stem cell transplant.[2]

Carcinogenicity: In animal studies, preneoplastic and neoplastic lesions (e.g., hepatocellular adenomas, oval cell hyperplasia, and altered cell foci in the liver) occurred at lower exposures (approximately one third lower) than exposures seen following human clinical exposure.[2]

Mutagenicity: Mutagenic in Ames test. Inotuzumab ozogamicin is clastogenic in mammalian *in vivo* chromosome tests.[2]

Fertility: In animal studies, female subjects experienced ovarian, uterine, vaginal, and mammary gland atrophy following exposure. Male subjects experienced testicular degeneration with hypospermia and atrophy of prostatic and seminal vesicles.[2]

Pregnancy: In animal studies, embryo-fetal toxicity was observed (e.g., increased resorptions, decreased viable embryos, and fetal growth retardation). For females of reproductive potential, pregnancy testing should be considered prior to treatment. Contraception is recommended during treatment and for at least eight months after the last dose of inotuzumab ozogamicin. In males with female partners of reproductive potential, contraception is recommended during treatment and for at least five months after the last dose of inotuzumab ozogamicin.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women may begin breastfeeding two months after the last dose of inotuzumab ozogamicin.[2]

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[8,9].

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (30-36%, severe 19-24%)[2,10]
	febrile neutropenia (26-27%)[2,10]
	leukopenia (27-35%, severe 25-33%)[2,10]
	lymphopenia (17-18%, severe 16%)[2,10]
	neutropenia (48-49%, severe 46-48%)[2,10]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pancytopenia (2%, severe 1%)
	thrombocytopenia (45-51%, severe 37-42%)[2,10]
cardiac	tachycardia (4%)[10]
gastrointestinal	*emetogenic potential:* low[11]
	abdominal distention (6%)
	abdominal pain (14-23%, severe 2-3%)[2,10]
	ascites (4%, severe 2%)
	constipation (16-17%)[2,10]
	diarrhea (17-18%, severe ≤1%)[2,10]
	nausea (31-32%, severe 2%)[2,10]
	stomatitis (13%, severe 2%)
	vomiting (15-17%, severe ≤1%)[2,10]
general disorders and administration site conditions	*extravasation hazard:* none[12,13]
	chills (10-11%)[2,10]
	edema, peripheral (9%, severe <1%)[10]
	fatigue (22-35%, severe 3-5%)[2,10]
	infusion related reaction (2%); see paragraph following **Side Effects** table
	pyrexia (27-32%, severe 3-4%)[2,10]
hepatobiliary	***hepatotoxicity*** (14%)[3]
	venoocclusive disease/sinusoidal obstruction syndrome (3-23%, severe 2-9%)[2,3,10]; see paragraph following **Side Effects** table
infections and infestations	***infection*** (48%, severe 28%); including fatal cases of pneumonia and sepsis
investigations	alkaline phosphatase increase (12-57%, severe 1-2%)[2,10]
	ALT increase (14-49%, severe 3-4%)[2,10]; see paragraph following **Side Effects** table
	amylase increase (5-15%, severe 2%)
	AST increase (20-71%, severe 4-5%)[2,10]; see paragraph following **Side Effects** table
	bilirubin increase (15-36%, severe 4-5%)[2,10]; see paragraph following **Side Effects** table
	gamma-glutamyltransferase increase (17-67%, severe 9-18%)[2,10]
	lipase increase (9-32%, severe 4-13%)
	PR interval prolongation (6%)
	QTc interval prolongation (1%)
metabolism and nutrition	appetite decrease (9-12%, severe 1%)[2,10]
	hyperuricemia (4-16%, severe 2-3%); see paragraph following **Side Effects** table
	hypocalcemia (8%, severe 1%)[10]
	hypokalemia (17%, severe 7%)[10]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	tumour lysis syndrome (1-2%, severe ≤2%)[2,10]; see paragraph following **Side Effects** table
musculoskeletal and connective tissue	pain in extremity (9%)[10]
nervous system	dizziness (9%)[10]
	headache (28%, severe 1-2%)[2,10]
psychiatric	insomnia (15%)[10]
renal and urinary	acute renal failure (1%, severe <1%)[10]
respiratory, thoracic and mediastinal	cough (11%)[10]
	dyspnea (5%, severe <1%)[10]
	epistaxis (15%, severe <1%)[10]
skin and subcutaneous tissue	rash (9%)[10]
vascular	***hemorrhage*** (33%, severe ≤33%)[2,3]
	hypotension (8%)[10]

Adapted from standard reference[2] unless specified otherwise.

Hepatotoxicity has been reported, including grade 3-4 elevations in AST, ALT, and bilirubin and severe ***venoocclusive disease***/sinusoidal obstruction syndrome (VOD). VOD is sometimes fatal. Patients are at greater risk of VOD if they receive HSCT following inotuzumab ozogamicin, particularly if bilirubin is elevated prior to HSCT or a conditioning regimen with two alkylating agents is used. Additional risk factors may include: ongoing/ prior liver disease, prior HSCT, increased age, later salvage lines, and a higher number of inotuzumab ozogamicin treatment cycles. Monitor all patients for elevations in transaminases and alkaline phosphatase plus signs of VOD (e.g., increased bilirubin, hepatomegaly, ascites, rapid weight gain). Dose reduction, treatment interruption, or permanent discontinuation may be required to manage elevated liver panel values. Permanently discontinue inotuzumab ozogamicin if VOD develops.[2,3]

Hyperuricemia may result from cell lysis by inotuzumab ozogamicin and may lead to electrolyte disturbances or acute renal failure.[14] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[15]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 mL/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg PO initially, then 300 mg PO q6h x6 doses, then 300 mg PO daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[16] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[17]

Infusion-related reactions are reported. Fever, chills, rash, and breathing difficulties are generally grade 2 or lower and usually occur shortly after the end of the cycle one infusions. Premedication with a corticosteroid, antihistamine, and antipyretic is recommended for all patients prior to each dose for all cycles of inotuzumab ozogamicin. For management of hypersensitivity reactions, see BC Cancer Protocol SCDRUGRX ***Management of Hypersensitivity***

Reactions to Chemotherapeutic Agents. Permanently discontinue inotuzumab ozogamicin for a severe or life-threatening reaction.[2]

A higher ***post-HSCT non-relapse mortality*** rate has been reported in patients receiving inotuzumab ozogamicin, most commonly related to venoocclusive disease or infection. Close monitoring for signs/symptoms of infection and other toxicity is advised post-HSCT.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
granulocyte colony-stimulating factors[2]	no effect on inotuzumab ozogamicin clearance		
hydroxyurea[2]	no effect on inotuzumab ozogamicin clearance		

Inotuzumab ozogamicin is associated with PR and QTc prolongation. Avoid concurrent therapy with other drugs associated with PR/QTc prolongation, torsades de pointes, and/or drugs that disrupt electrolyte levels. If concurrent therapy is unavoidable, monitor for PR/QTprolongation and/or cardiac arrhythmias.[2]

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide is a substrate of P-glycoprotein; however, no effect is seen on inotuzumab ozogamicin clearance when it is used in combination with inhibitors of P-glycoprotein clinically.[2]

SUPPLY AND STORAGE:

***Injection*:** Pfizer Canada Inc. supplies inotuzumab ozogamicin as 0.9 mg vials of sterile lyophilized cake or 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.

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: To maintain drug efficacy, protect inotuzumab ozogamicin from ***fluorescent and UV light during storage, preparation, and administration.*** Inotuzumab ozogamicin contains an acid-cleavable linker which binds inotuzumab to calicheamicin. This linker is sensitive to fluorescent and ultraviolet light. Light exposure can degrade the linker, causing release of unconjugated calicheamicin. Therefore, the antibody and calicheamicin must remain linked prior to receptor binding to maintain drug efficacy. NOTE: During preparation, light protection of the syringe is required if the reconstituted drug is not immediately added to the infusion bag. In addition, the IV line requires light protection if administration of the drug cannot be completed within one hour of hanging the bag.[2,18]

Compatibility: consult detailed reference

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 60 minutes***[2,19]

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. Dosing schedules 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[2,10,19]*:*

Cycle Length:

3-4 weeks:

Cycle 1:
0.8 mg/m^2 IV for one dose on day 1, then 0.5 mg/m^2 IV for one dose on days 8 and 15
(total dose per cycle 1.8 mg/m^2)

Cycle 2-6:
0.5-0.8 mg/m^2 IV for one dose on day 1, then 0.5 mg/m^2 IV for one dose on days 8 and 15
(total dose per cycle 1.5-1.8 mg/m^2)

Concurrent radiation: no information found

Dosage in myelosuppression[2]*:* dose modifications are dependent on baseline/previous cycle ANC and platelet counts AND on the duration of any dose interruptions; modify according to protocol by which patient is being treated

Dosage in renal failure[2]*:*

CrCl ≥15 mL/min: no adjustment required
CrCl <15 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]*:*

bilirubin ≤1.5 x ULN and AST/ALT ≤2.5 x ULN: no adjustment required
bilirubin >1.5 x ULN and AST/ALT >2.5 x ULN: no information found

Dosage in dialysis: no information found

Children: safety and efficacy have not been established[2]

REFERENCES:

1. Betts AM, Haddish-Berhane N, Tolsma J, et al. Preclinical to clinical translation of antibody-drug conjugates using PK/PD modeling: a retrospective analysis of inotuzumab ozogamicin. AAPS J 2016;18(5):1101-1116.
2. Pfizer Canada Inc. BESPONSA® product monograph. Kirkland, Quebec; 15 March 2018.
3. Lexi-Drugs Drug Information® (database on the Internet). Inotuzumab ozogamicin. Lexi-Comp Inc., 29 September 2018. Available at: http://online.lexi.com. Accessed 1 October 2018.
4. AHFS Drug Information® (database on the Internet). Inotuzumab ozogamicin. Lexi-Comp Inc., 27 February 2018. Available at: http://online.lexi.com. Accessed 1 October 2018.
5. Paul S, Rausch CR, Kantarjian H, et al. Treatment of adult acute lymphoblastic leukemia with inotuzumab ozogamicin. Future Oncology 2017;13(25):2233-2242.
6. Choudhry A, O'Brien SM. Inotuzumab ozogamicin for the treatment of patients with acute lymphocytic leukemia. Drugs of Today 2017;53(12):653-665.
7. Pfizer Canada Inc. Personal communication. Pfizer Canada Medical Information; 20 November 2018.
8. David Sanford MD. Personal communication. BC Cancer Leukemia and Bone Marrow Transplant Tumour Group; 28 November 2018.
9. Kathryn Lacaria. Personal communication. Leukemia/Bone Marrow Transplant Program of British Columbia, Vancouver General Hospital; 7 January 2019.
10. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016;375(8):740-753.
11. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 Mar 2012.
12. 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; January 2016.
13. Pfizer Canada Inc. Personal communication. Pfizer Canada Medical Information; 6 November 2018.
14. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 2640.
15. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. 4th ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2003. p. 27.
16. Sanofi-Synthelabo. FASTURTEC® product information. Markham, Ontario; 2004.
17. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. E-Edition ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2010. p. 93-94.
18. Pfizer Canada Inc. Personal communication. Pfizer Canada Medical Information; 26 November 2018.
19. BC Cancer Leukemia and Bone Marrow Transplant Tumour Group. (ULKINOZ) BC Cancer Protocol Summary for Treatment of Refractory or Relapsed Pre-B Cell Acute Lymphoblastic Leukemia with Inotuzumab Ozogamicin. Vancouver, British Columbia: BC Cancer; 1 Jun 2019.