DRUG NAME: Obinutuzumab

SYNONYM(S): afutuzumab, GA101, R7159, RG7159, RO5072759[1]

COMMON TRADE NAME(S): GAZYVA®

CLASSIFICATION: monoclonal antibody

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

MECHANISM OF ACTION:

Obinutuzumab is a humanized recombinant type II anti-CD20 monoclonal antibody. It specifically targets the CD20 transmembrane antigen on malignant and non-malignant pre-B and mature B-lymphocytes. It does not target the hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. Obinutuzumab induces cell death and mediates antibody dependent cellular cytotoxicity. Obinutuzumab is an immunosuppressive agent.[2]

PHARMACOKINETICS:

Distribution	no information found regarding tissue distribution	
	cross blood brain barrier?	no information found
	volume of distribution[1-3]	4-16 L
	plasma protein binding	no information found
Metabolism	mainly cleared by catabolism	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	linear and time-dependent nonlinear clearance, however nonlinear pathway diminishes following repeat administration[4]	
	urine	no information found
	feces	no information found
	terminal half life	24-30 days
	clearance	90-125 mL/day

Adapted from standard reference[2,3] unless specified otherwise.

USES:

Primary uses:

*Leukemia, chronic lymphocytic

*Lymphoma, non-Hodgkin's

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- ***Infusion reactions*** commonly occur with the first infusion; routine premedication is recommended for all infusions.[2]

- ***Reactivation of hepatitis B virus*** (HBV) has been reported, and in some cases resulting in fulminant hepatitis, hepatic failure and death.[2] HBV screening (HBsAg and anti-HBc) is suggested in all patients prior to initiation of obinutuzumab; if either test is positive, prophylaxis with lamivudine 100 mg/day orally is indicated during treatment with obinutuzumab and for 6 months after.[5,6]
- ***Hyperuricemia*** and ***tumour lysis syndrome*** can occur with obinutuzumab; patients with high tumour burden, high lymphocyte count (greater than 25 x 10^9/L), and/or renal impairment (creatinine clearance less than 70 mL/min) are most at risk.[7]
- ***Cardiovascular events***, such as myocardial infarction and dysrhythmias have been reported and are sometimes fatal; patients with pre-existing cardiac disease may experience worsening of their cardiovascular disease.[2]
- ***Live vaccines*** are not recommended during treatment or until B-cell recovery has occurred post-treatment; obinutuzumab can be started following vaccination once protective antibody titres are reached.[7]

Special populations: Patients 75 years old or greater and those with creatinine clearance less than 50 mL/min reportedly experience more serious adverse events than other patient groups.[2]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal studies, no adverse effects on male and female reproductive organs were observed.[2]

Pregnancy: FDA Pregnancy Category C.[8] Animal studies have shown fetal risks and there are no controlled studies in women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. An animal reproduction study showed no evidence of teratogenic effects, however infants exposed to obinutuzumab during gestation were born with a complete depletion of B-lymphocytes. B-cell counts and immunologic function were restored within 6 months of birth. Due to the potential depletion of B-cells in newborns exposed to obinutuzumab during pregnancy, B-cell counts should be monitored and vaccinations with live virus vaccines should be postponed until the infant's B-cell counts return to normal. Women of child-bearing potential should use effective contraception while on obinutuzumab and for 18 months after discontinuation of therapy.[2]

Breastfeeding is not recommended during obinutuzumab therapy and for 18 months after discontinuation of therapy. Animal studies have demonstrated the presence of obinutuzumab in breast milk.[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.[9,10] **Incidence data in the Side Effects table is based on combination therapy with chlorambucil.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (12-39%, severe 4-10%)[2,3]
	febrile neutropenia (3%, severe 2%)
	lymphocytopenia (1-84%, severe 4-40%)[2,3,8]
	neutropenia (38-78%, severe 33-48%)[2,3]; see paragraph following **Side Effects** table.
	thrombocytopenia (11-48%, severe 10-14%)[2,3,8]; see paragraph following **Side Effects** table
cardiac	atrial fibrillation (2%)
	cardiac failure, congestive (1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	exacerbation of cardiac disease (<1%)[2,8]
ear and labyrinth	vertigo (1%)
gastrointestinal	*emetogenic potential: rare*[11]
	abdominal pain (4-5%)
	constipation (7-8%)[2,3]
	diarrhea (10%, severe 2-3%)[2,3]
	dry mouth (2%)
	dyspepsia (3%)
	hemorrhoids (1%)
	nausea (13%)
	stomatitis (2%)
	vomiting (5%)
general disorders and administration site conditions	*extravasation hazard: none*[12]
	infusion-related reactions (53%, severe 17%)[13]; see paragraph following **Side Effects** table
	asthenia (8%)
	chest pain (2%)
	chills (2%)
	fatigue (7%, severe 1%)
	peripheral edema (3%)
	pyrexia (9-10%, severe <1%)[2,3]
infections and infestations	bronchitis (4%)
	cystitis (1%)
	hepatitis B virus reactivation; see paragraph following **Side Effects** table
	herpes simplex (2-3%)
	herpes zoster (2%)
	infection (1-38%, severe 9-12%)[2,4,8,14]; see paragraph following **Side Effects** table
	nasopharyngitis (6-7%, severe <1%)[2,3]
	pharyngitis (2%)
	pneumonia (5%, severe 3-4%)[2,14]
	respiratory tract infection (2-3%)
	rhinitis (2%)
	sepsis (1%, severe 1%)
	urinary tract infection (5-6%, severe 1-2%)[2,3]
investigations	***alkaline phosphatase increase*** (16-18%)[2,3]; see paragraph following **Side Effects** table
	ALT increase (1-28%, severe 2%)[2,3]; see paragraph following **Side Effects** table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	AST increase (27-29%, severe 1- 2%)[2,3,8]; see paragraph following **Side Effects** table
	creatinine increase (28-30%, severe <1%)[2,3]
	weight decrease (1%)
	weight increase (2%)
metabolism and nutrition	appetite decrease (3%)
	dehydration (1%)
	hyperglycemia (2%, severe 2%)
	hyperkalemia (2-33%, severe 1-5%)[2,3]
	hyperuricemia (3%); see paragraph following **Side Effects** table
	hypoalbuminemia (22-23%, severe <1%)[2,3]
	hypocalcemia (1-38%, severe 3%)[2,3]
	hypokalemia (13-15%, severe 1%)[2,3]
	hyponatremia (26-30%, severe 7-8%)[2,3]
	tumour lysis syndrome (4%, severe 2%), can occur within 12-24 hours after the first infusion; see paragraph following **Side Effects** table
musculoskeletal and connective tissue	arthralgia (5%)
	back pain (5%, severe <1%)[2,3]
	bone pain (2%)
	limb pain (3%)
	musculoskeletal pain (2-3%)
	muscle spasms (1%)
neoplasms	basal cell carcinoma (1%)
nervous system	dizziness (4%)
	dysgeusia (3%)
	headache (8%)
	paraesthesia (1%)
	progressive multifocal leukoencephalopathy [8]; see paragraph following **Side Effects** table
	restlessness (1%)
	thrombohemorrhagic event (1-4%, severe <1%)[2,8]
psychiatric	anxiety (1%)
	insomnia (3%)
renal and urinary	dysuria (1%)
	renal failure, acute (<1%)[2,8]
respiratory, thoracic and mediastinal	bronchitis, chronic (2%)
	cough (10%)
	dysphonia (1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dyspnea (2%)
	epistaxis (3%)
	laryngeal edema (<1%)[2,8]
	oropharyngeal pain (1%)
	pleural effusion (1%)
skin and subcutaneous tissue	alopecia (2%)
	dry skin (1%)
	excoriation (1%)
	pruritis (4%)
	rash (3%)
vascular	hypertension (3%, severe 1%)
	hypotension (1%)

Adapted from standard reference[2] unless specified otherwise.

Hematologic events including ***neutropenia*** and ***thrombocytopenia*** have been reported. Antimicrobial, antiviral, and antifungal prophylaxis are recommended for neutropenic patients; granulocyte colony stimulating factors should be considered as needed. Febrile neutropenia, worsening of existing neutropenia, and prolonged (lasting more than 28 days) or late onset neutropenia (occurring 28 days or later after end of treatment) have also been observed. Thrombocytopenia and fatal hemorrhagic events such as cerebrovascular accident, subdural hematoma and stroke have been reported, although a clear relationship between thrombocytopenia and hemorrhagic events has not been established. Acute thrombocytopenia can occur within 24 hours after obinutuzumab infusion; consider holding concomitant medications which may increase bleeding risk. Platelet transfusion may be needed.[2]

Hepatic enzyme elevations are reported most frequently within 24-48 hours of the first infusion and may occur concurrently with infusion reactions or tumour lysis syndrome. Elevated enzymes may also be due to the medications given to prevent infusion reactions (e.g., acetaminophen). For patients who develop hepatoxicity, consider treatment interruption or discontinuation.[3]

Hepatitis B virus (HBV) reactivation can occur in patients treated with obinutuzumab, and in some cases may result in fulminant hepatitis, hepatic failure, and death. HBV reactivation has been reported in patients who are HBsAg positive, patients who are HBsAg negative but are anti-Hbc positive, and also patients whose hepatitis B infection has resolved (i.e., HBsAg negative, anti-HBc positive, and anti-HBs positive). HBV reactivation is characterized by a rapid increase in serum HBV DNA levels or detection of HBsAg in patients who were previously HBsAg negative and anti-HBc positive and is often followed by hepatitis (i.e., increased transaminases). In severe cases, patient may progress to liver failure and death. HBV reactivation has been reported with other anti-CD20 antibodies and may occur more than 12 months after completion of therapy. All patients should be screened for HBV infection prior to initiating treatment with obinutuzumab. Consider referral to a physician specializing in managing hepatitis B for patients who test positive during screening. Discontinue obinutuzumab in patients who experience reactivation of HBV and initiate antiviral treatment. There is insufficient data regarding the safety of resuming obinutuzumab in patients who develop HBV reactivation.[2,4]

Hyperuricemia may result from cell lysis by obinutuzumab and may lead to electrolyte disturbances or acute renal failure.[15] 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 [16]:

- aggressive hydration: 3 L/m^2/24 hours 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 x 6 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.[17] 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.[18]

Infections, including bacterial, fungal, and new or reactivated viral infections, can occur during and after treatment with obinutuzumab. Infections are sometimes fatal. Obinutuzumab should not be given to patients with an active infection; use cautiously in patients with recurring or chronic infections.[2]

Infusion-related reactions, including anaphylaxis, have been reported.[2] Reactions can occur within 24 hours of receiving obinutuzumab; occurring more frequently with the first infusion and decreasing with each subsequent infusion.[2,3] When loading dose was delivered as 25 mg on day 1 and 975 mg on day 2 of cycle 1 treatment,[19] reactions occurred most commonly within 1-2 hours after start of infusion on the first dose and after more than 5 hours on the second dose.[20] Symptoms may include nausea, chills, hypotension, pyrexia, vomiting, dyspnea, flushing, hypertension, headache, tachycardia, and diarrhea. Severe infusion reactions can present as bronchospasms, larynx and throat irritation, wheezing, laryngeal edema, and atrial fibrillation. Patients with a high tumour burden may be at an increased risk of severe infusion reactions. If a reaction occurs, interrupt or decrease the rate of the infusion and institute appropriate medical management. Dividing the first treatment over 2 days and giving premedications (i.e., analgesic/anti-pyretic, antihistamine, and corticosteroids such as dexamethasone, prednisone, or methylprednisolone) may decrease the incidence and severity of infusion reactions. Hydrocortisone has not been effective in reducing the rate of infusion-related reactions and is not recommended as a premedication. Hypotension may occur during obinutuzumab infusion; monitor patients with pre-existing cardiac or pulmonary conditions. Consider holding antihypertensive medications 12 hours prior to, during, and for one hour after the infusion. Obinutuzumab should be permanently discontinued if patients experience[2]:

- acute life-threatening respiratory symptoms,
- a grade 4 infusion reaction, or
- a second occurrence of a grade 3 infusion reaction (after resuming a first infusion or during a subsequent infusion)

For management of hypersensitivity reactions, refer to BC Cancer Protocol SCDRUGRX ***Management of Hypersensitivity Reactions to Chemotherapeutic Agents***.

Progressive multifocal leukoencephalopathy (PML), a severe CNS disease that is caused by reactivation of the JC virus,[21] has also been reported with obinutuzumab.[2] Any patients presenting with new neurologic symptoms such as confusion, vision changes, changes in speech, difficulty walking, dizziness, or vertigo should be evaluated for PML.[4] Consider consultation with a neurologist, as well as a brain MRI and cerebral spinal fluid testing for JC viral DNA. Withhold obinutuzumab during investigation of potential PML; permanently discontinue obinutuzumab after confirmed diagnosis.[2]

INTERACTIONS: no documented interactions

SUPPLY AND STORAGE:

***Injection*:** Hoffman-La Roche supplies obinutuzumab as a preservative-free liquid concentrate in 1000 mg/40 mL single-use vials. Refrigerate. Protect from light. Do not shake.[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:
- Do not prepare or administer using dextrose containing solutions.[2]
- For regimens where cycle 1 doses are administered as split doses on days 1 and 2: infusion bags for days 1 and 2 are prepared at the same time from a single obinutuzumab vial (100 mg for Day 1 and 900 mg for Day 2)[7]; refer to **Dosage Guidelines.**

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[2]</td><td>not recommended</td></tr>
<tr><td>Intermittent infusion[5-7,22]</td><td>Refer to protocol by which patient is being treated. Administration schedules depend on disease, cycle, and occurrence of infusion reactions. In the absence of other guidelines, the following incremental infusion rate may be used.
<table>
<tr><th></th><th>Dose</th><th>Initial rate</th><th>Rate increment[a]</th><th>Maximum rate</th></tr>
<tr><td>cycle 1, day 1 (split dosing)</td><td>100 mg</td><td>25 mg/h</td><td>N/A</td><td>25 mg/h</td></tr>
<tr><td>cycle 1, day 2 (split dosing)</td><td>900 mg</td><td>50 mg/h</td><td>50 mg/h every 30 min</td><td>400 mg/h</td></tr>
<tr><td>cycle 1, day 1</td><td>1000 mg</td><td>50 mg/h</td><td>50 mg/h every 30 min</td><td>400 mg/h</td></tr>
<tr><td>cycle 1, days 8 and 15</td><td>1000 mg</td><td>100 mg/h</td><td>100 mg/h every 30 min</td><td>400 mg/h</td></tr>
<tr><td>cycle 2-8</td><td>1000 mg</td><td>100 mg/h</td><td>100 mg/h every 30 min</td><td>400 mg/h</td></tr>
</table></td></tr>
<tr><td>Continuous infusion</td><td>no information found</td></tr>
<tr><td>Intraperitoneal</td><td>no information found</td></tr>
<tr><td>Intrapleural</td><td>no information found</td></tr>
<tr><td>Intrathecal</td><td>no information found</td></tr>
<tr><td>Intra-arterial</td><td>no information found</td></tr>
<tr><td>Intravesical</td><td>no information found</td></tr>
</table>

[a]escalate only in the absence of infusion reactions/hypersensitivity

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).

***Adults*:**

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

Intravenous:	***4 weeks***[5,14,19,22]:	**Cycle 1** (split dosing): ***100 mg IV for one dose on day 1, 900 mg IV for one dose on day 2,*** then ***1000 mg IV for one dose on days 8 and 15*** (total dose per cycle = 3000 mg) **Cycles 2-6**: ***1000 mg IV for one dose on day 1*** (total dose per cycle = 1000 mg) Dose reductions are not recommended.
	3-***4 weeks***[6,22,23]:	**Cycle 1**: ***1000 mg IV for one dose on days 1, 8 and 15*** (total dose per cycle = 3000 mg) **Cycles 2-8**: ***1000 mg IV for one dose on day 1*** (total dose per cycle = 1000 mg) Dose reductions are not recommended.
	2 months[22]	1000 mg IV for one dose on day 1 (total dose per cycle = 1000 mg)
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated	
Dosage in renal failure[2]:	• no dose reduction for CrCl > 30 mL/min; • no information found for CrCl < 30 mL/min	

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:	no information found
Dosage in dialysis:	no information found
Children:	no information found

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