Drug Monograph

A - Drug Name

oBINutuzumab

COMMON TRADE NAME(S): Gazyva®

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B - Mechanism of Action and Pharmacokinetics

Obinutuzumab is a recombinant IgG1 monoclonal antibody that targets CD20 expressed on the surface of pre-B and mature B-lymphocytes. The drug promotes cell death via antibody-dependent cellular cytotoxicity and phagocytosis and via activation of the complement cascade.

Distribution	No information found.	
Metabolism	Antibodies are primarily cleared via catabolism.	
Elimination	Half-life	24 days (mean elimination)

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C - Indications and Status

Health Canada Approvals:

- In combination with chlorambucil for previously untreated chronic lymphocytic leukemia (CLL)
- In combination with bendamustine, followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to a rituximab-containing

regimen
- In combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving a response, for the treatment of patients with previously untreated stage II bulky (>7cm), III or IV follicular lymphoma

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following adverse effects were reported in the phase 3 clinical trial in CLL in which obinutuzumab was given in combination with chlorambucil, where the incidence was 2% or higher than for chlorambucil alone. Severe or life-threatening events are also reported from other studies and post-marketing reports.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (2%)	I E
	Arterial thromboembolism (2%)	E
	Hypertension (4%)	E
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (2%)	E
Gastrointestinal	Dry mouth (2%)	E
	GI perforation (rare)	E D
General	Fever (10%)	E
	Flu-like symptoms (2%)	E
Hematological	Hemolysis (rare)	E
	Myelosuppression ± infection, bleeding (35%) (severe, including viral reactivation, opportunistic infections)	E
Hepatobiliary	↑ LFTs (29%) (may be severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Anaphylaxis (rare)	I
	Infusion related reaction (69%) (21% severe)	I
	Serum sickness (rare)	E D
Metabolic /	Hyperglycemia (2%)	E

Endocrine		
	Tumor lysis syndrome (4%)	E
Musculoskeletal	Musculoskeletal pain (5%)	E
Neoplastic	Secondary malignancy (2%)	L
Nervous System	Leukoencephalopathy (PML; rare)	E
Renal	Creatinine increased (30%) (may be severe)	E
Respiratory	Cough, dyspnea (10%)	E
	Pneumonitis (rare)	E
Vascular	Capillary leak syndrome (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)

The most common side effects for oBINutuzumab include infusion related reaction, myelosuppression ± infection, bleeding, ↑ lfts, creatinine increased, nausea, vomiting, cough, dyspnea, diarrhea, fever, abnormal electrolyte(s) and fatigue.

Infusion-related reactions (IRs), as well as anaphylaxis or delayed onset serum sickness, are common and may not be easily distinguished from each other. Most reactions, including life-threatening events, occurred during the infusion of the first 1000 mg and are more common with high bulk disease. Dividing the first dose over two days and use of premedication reduce the frequency and severity of these. Patients with pre-existing cardiac or pulmonary conditions are at increased risk and should be monitored closely.

Serious **cardiovascular events** have been reported as part of infusion reactions or worsening of pre-existing cardiovascular disease. Patients with high tumour burden (e.g. peripheral lymphocyte count in CLL >25 x 10^9/L), pre-existing cardiac or pulmonary conditions should be monitored closely.

Fatal **hemorrhagic events** have been reported during the first cycle and may or may not be related to thrombocytopenia. Consider withholding concomitant medications which may increase bleeding risk, especially during the first cycle. Severe and/or prolonged **myelosuppression,** including **thrombocytopenia** has been reported during treatment or a month or more after treatment completion. There is a high risk of infections especially when given in combination with chemotherapy. A higher incidence of severe, life-threatening and fatal infections was observed in patients treated in combination with bendamustine as compared to combinations with CHOP or CVP.

Patients at risk of **tumour lysis syndrome** (i.e. high tumour burden, renal impairment CrCl <70mL/min, or WBC > 25 x 10^9/L) should have appropriate prophylaxis (see section E) and renal function, potassium and uric acid values should be monitored closely during initial days of treatment.

Hepatitis B infection and reactivation have been described, even in patients who are surface antigen negative, several months after treatment completion and may be fulminant. Hepatitis B testing should be performed in all patients before starting treatment. Any patient who shows evidence of hepatitis B infection (surface antigen positive, or surface antigen negative but core antibody positive) should be referred to a hepatologist regarding HBV therapy and monitoring.

JC virus infection and **PML** have been reported and may present with nonspecific neurological symptoms. PML should be considered in such cases and treatment held while the patient is investigated. Discontinue if confirmed.

Anti-drug antibodies have been detected but are of uncertain clinical significance.

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E - Dosing

Hepatitis B screening should be performed prior to treatment for all patients.

Patients at risk for tumour lysis syndrome should receive adequate hydration and uricostatics or alternatives starting 12 to 24 hours prior to infusion. Consider splitting the first treatment over two days for patients with high tumour burden.

Consider withholding antihypertensives (if applicable) 12 hours prior to infusion, during infusion and for the first hour after drug administration, and withholding concomitant medications that increase bleeding risk, especially in the first cycle. Patients with neutropenia should receive antimicrobial prophylaxis; consider G-CSF, antiviral and antifungal prophylaxis.

Adults:

Premedications (prophylaxis for infusion reactions):

Table 1:

Treatment cycle, day	Patients	Premedication
CLL: cycle 1, days 1 & 2 NHL (FL): cycle 1, day 1	All	• IV corticosteroid*^ at least 1 hr prior to infusion • PO antipyretic** at least 30 min prior to infusion • antihistamine*** at least

		30 min prior to infusion
CLL & NHL (FL) subsequent infusions	Patients with no IR during previous infusion	• PO antipyretic** at least 30 min prior to infusion
	Patients with grade 1 or 2 IR with previous infusion	• PO antipyretic** at least 30 min prior to infusion • antihistamine*** at least 30 min prior to infusion
	Patients with grade 3 IR with previous infusion OR patients with lymphocyte counts > 25 x 10^9/L prior to next treatment	• IV corticosteroid**^ at least 1 hr prior to infusion • PO antipyretic** at least 30 min prior to infusion • antihistamine*** at least 30 min prior to infusion

* e.g. 80 mg methylprednisolone or 20 mg dexamethasone. Hydrocortisone is not recommended as it has not been effective in reducing IR rates.

** e.g. 1000 mg acetaminophen

*** e.g. 50 mg diphenhydramine

^ If a corticosteroid-containing chemotherapy regimen is given on the same day as obinutuzumab, the corticosteroid can be given as PO if given at least 1 hour prior to obinutuzumab, in which case additional IV corticosteroid as premedication is not required

For CLL in combination with chlorambucil

Refer to CHLO+OBIN regimen for chlorambucil dosing

obinutuzumab IV (refer to table 2)

Q28 days for 6 cycles

Table 2: Obintutuzumab Dose and Infusion rate (CLL)

Treatment cycle	Obinutuzumab dose*	Infusion rate
Cycle 1, day 1	100 mg	25 mg/hr over 4 hours

Cycle 1, day 2 (or day 1 continued)	900 mg	50 mg/hr if no IR on day 1. May escalate as tolerated by 50 mg/hr q 30 min to max of 400 mg/hr. 25 mg/hr if previous IR. May escalate as tolerated by up to 50 mg/hr q 30 min to max of 400 mg/hr.
Cycle 1, day 8	1000 mg	100 mg/hr if no IR at rates ≥ 100mg/hr on day 2. May escalate as tolerated by 100 mg/hr q 30 min to max of 400 mg/hr. 50 mg/hr if previous IR. May escalate as tolerated by 50 mg/hr q 30 min to max of 400 mg/hr.
Cycle 1, day 15	1000 mg	
Cycles 2 to 6, day 1	1000 mg q 28 days	

*Two infusion bags should be prepared for the first 1000 mg infusion (100 mg for day 1, 900 mg for day 2). If the first bag is completed without needing modifications of infusion rate, the second bag may also be administered on day 1 without a dose delay, if possible.

For follicular lymphoma (FL) in combination with bendamustine

Induction (q28 days for 6 cycles):

Refer to BEND+OBIN regimen for bendamustine dosing. See table 3 for obinutuzumab IV dosing.

For follicular lymphoma in combination with CHOP

Induction (q21 days for 6 CHOP+OBIN cycles, followed by 2 OBIN cycles)†:
Refer to CHOP+OBIN regimen for chemotherapy dosing. See table 3 for obinutuzumab IV dosing.

For follicular lymphoma in combination with CVP:

Induction (q21 days for 8 cycles)†:
Refer to CVP+OBIN regimen for chemotherapy dosing. See table 3 for obinutuzumab IV dosing.

† NDFP funds up to 6 cycles of obinutuzumab in relapsed/refractory indolent lymphoma. Refer to obintuzumab NDFP form.

For Follicular Lymphoma - Maintenance (q2 months):

Patients who respond to induction or have stable disease may continue obinutuzumab monotherapy every 2 months until disease progression or for up to 2 years, whichever occurs first (see table 3)

Table 3: Obinutuzumab dose and infusion rate (FL)

Treatment cycle	Obinutuzumab dose	Infusion rate
Cycle 1, day 1	1000 mg	50 mg/hr. May escalate as tolerated by 50 mg/hr q30 min to max of 400 mg/hr.
Cycle 1, days 8 & 15; Cycles 2 onwards, day 1; Maintenance (q2 months)	1000mg	100 mg/hr if IR ≤ grade 1 at rates ≥ 100mg/hr on day 1. May escalate as tolerated by 100 mg/hr q30 min to max of 400 mg/hr. 50 mg/hr if previous grade 2 or 3 IR. May escalate as tolerated by 50 mg/hr q30 min to max of 400 mg/hr.

Dosage with Toxicity:

No dose reductions are recommended for obinutuzumab. The infusion may be discontinued, held or its rate reduced as described in table 4. See the specific chemotherapy combination regimen monographs for dose modifications for combination therapy.

Table 4:

Toxicity	Obinutuzumab dose*, **
Grade 4 hematologic toxicity, febrile neutropenia or thrombocytopenic bleeding	Consider hold until ≤ grade 2, restart at usual dose. If no recovery within 4 weeks, discontinue.
Grade 2 or 3 related organ/non-hematologic toxicity	Hold until ≤ grade 1. If no recovery within 4 weeks, discontinue.
Grade 4 related organ/non-hematologic toxicity	Discontinue
Viral hepatitis or other serious infections; reactivation of hepatitis B	Discontinue
Suspected PML	Hold and refer to neurologist for diagnosis and treatment. If confirmed, discontinue.
Serum sickness	Discontinue

*Missed doses may be administered later at physician discretion; the planned treatment interval should then be maintained between doses.

**Hold up to 4 weeks. Before retreatment, major organ toxicities should recover to ≤ grade 1 (or as specified in table 2), platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x 10^9/L.

Table 5: 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, continue infusion. • If IR does not recur, may escalate the infusion rate at increments appropriate for the treatment dose (see Table 2 & 3). For CLL patients receiving the cycle 1, day 1 dose split over 2 days, day 1 infusion rate may be increased to 25mg/hr after 1 hour (but should not exceed this rate)	• For CLL patients: see Table 2 • For FL patients: see Table 3
3	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Once symptoms have resolved, restart the infusion at no more than half the previous rate (at which the IR occurred). • If IR does not recur, may escalate the infusion rate as outlined above for grade 1-2 IRs.	*If a grade 3 IR recurs for the 2nd time, discontinue permanently (do not re-challenge).
4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with Hepatic Impairment:

Safety and efficacy have not been established in patients with hepatic impairment.

Dosage with Renal Impairment:

Patients who have a creatinine clearance < 50mL/min in the pivotal study experienced more serious adverse events, including fatal ones, than those with creatinine ≥ 50 mL/min.

Creatinine clearance (mL/min)	Obinutuzumab dose
> 50	No dose adjustment
30-50	No dose adjustment; use with caution
<30	No data

Dosage in the elderly:

No dose adjustment is required. CLL patients ≥ 75 years and NHL patients ≥ 65 years of age experienced more serious adverse effects than younger patients. No efficacy differences were observed between older and younger patients.

Children:

Safety and efficacy have not been established in children under 18.

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F - Administration Guidelines

- Obinutuzumab should be administered only as an IV infusion through a dedicated line. **Do not administer as an IV push or bolus.**
- Withdraw required amount of diluent from vial and dilute in 250 ml PVC or non-PVC polyolefin bags containing 0.9% sodium chloride. See product monograph for details.
- For CLL, the initial 1000 mg dose should be prepared in two infusion bags of different sizes (i.e. 100 mg in 100 mL and 900 mg in 250 mL NS) to ensure differentiation of the 100 mg dose for day 1 and the 900 mg dose for day 2 (or day 1 continued).
- Gently invert the IV bag to mix. Do not shake.
- If a planned dose is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval should then be maintained between doses.

- Compatible with sodium chloride 0.9%. Do not mix with other IV solutions.
- Also compatible with the following IV bags and sets:
  - polyethylene, polypropylene bags
  - PVC, polyurethane or polyethylene infusion sets
  - polyetherurethane catheters
  - optional inline filters with polyethersulfon product contact surfaces
  - 3-way stopcock infusion aid made from polycarbonate
- Store vials between 2° to 8°C; protect 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:

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

Other Warnings/Precautions:

- Obinutuzumab should not be given in the presence of an active infection.
- Avoid live vaccines during treatment and until B-cell recovery. Following vaccination, do not start obinutuzumab until protective antibody titres have been reached.
- Use with extreme caution in patients who are positive for hepatitis
- Use with caution in patients with a history of recurring or chronic infections.
- Patients with a history of cardiovascular or respiratory disease should be monitored closely during and after infusions. Use caution when hydrating patients with history of cardiovascular disease, to prevent fluid overload
- Patients at acute risk of hypertensive crisis should be assessed for the risk vs benefit of withholding anti-hypertensives. If deemed clinically appropriate, hold antihypertensive medications for 12 hours prior to, during, and for the first hour after obinutuzumab infusion.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Teratogenicity: Unlikely
- Crosses placental barrier: Yes
  Obinutuzumab is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 18 months after the last dose. In case of exposure during pregnancy, newborns should be monitored for B-cell depletion and live

vaccines postponed until B cell recovery.

- Excretion into breast milk: Yes
  Breastfeeding is not recommended during treatment and for at least 18 months after the last dose.
- Fertility effects: Unknown

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H - Interactions

Formal drug interaction studies have not been conducted.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that cause immunosuppression (e.g. leflunomide, etanercept, clozapine, other antineoplastics)	↑ risk of myelosuppression, infections	Additive	Caution; monitor closely or avoid, if possible

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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
CBC	Baseline, before each dose and as clinically indicated following treatment completion
Liver and renal function tests, electrolytes	Baseline and prior to each cycle
Cardiac tests for all patients with cardiac risk factors	Baseline and as clinically indicated
Hepatitis B screening prior to treatment for all patients. Monitor for signs and symptoms of hepatitis B during treatment. Seropositive patients should see hepatologist and be closely monitored for several months after the last infusion.	
Infusion-related reactions	During and after each infusion

Clinical toxicity assessment for hypersensitivity, tumour lysis syndrome, infection, bleeding, neurologic, respiratory, thromboembolism, GI and cardiac 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

New Drug Funding Program (NDFP Website)

- Obinutuzumab - Previously Untreated Chronic Lymphocytic Leukemia
- Obinutuzumab - In Combination with Chemotherapy for Refractory Follicular Lymphoma
- Obinutuzumab - Maintenance Treatment for Refractory Follicular Lymphoma
- Obinutuzumab - in Combination with Venetoclax for Previously Untreated Chronic Lymphocytic Leukemia

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K - References

Product monograph: Gazyva (obinutuzumab). Hoffman-La Roche Ltd. July 3, 2018.

U.S. prescribing information: Gazyva (obinutuzumab). Genentech Inc. November 2013.

May 2022 Added NDFP form

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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