Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

OBIN(MNT) Regimen

oBINutuzumab (Maintenance)

Disease Site	Hematologic - Lymphoma - Non-Hodgkin's Low Grade
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	Maintenance treatment in patients with follicular lymphoma† who have disease response to or have stable disease after induction treatment with obinutuzumab plus chemotherapy (i.e. the initial 6 treatment cycles) † indolent lymphoma histologies other than follicular lymphoma (excluding CLL and mantle cell lymphoma) may be eligible for obinutuzumab funding (refer to NDFP form)
Supplementary Public Funding	**oBINutuzumab** New Drug Funding Program (Obinutuzumab - Maintenance Treatment for Refractory Follicular Lymphoma)

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B - Drug Regimen

Obinutuzumab maintenance should be initiated within 4 months of the last dose of obinutuzumab induction therapy (see NDFP form).

oBINutuzumab	1000 mg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 2 MONTHS

Until disease progression or for up to 2 years (maximum 12 doses), whichever occurs first.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Patients at risk for tumour lysis syndrome should receive adequate hydration and uricostatics or alternative starting 12 to 24 hours prior to infusion.

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 induction cycle.

Patients with neutropenia should receive antimicrobial prophylaxis; consider use of G-CSF, antiviral and antifungal prophylaxis.

Premedications (prophylaxis for infusion reactions):

Patients	Premedication
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

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

No dose reductions are recommended for obinutuzumab. The infusion may be discontinued, held or its rate reduced as described in Table 1 & 2.

Table 1:

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;	Discontinue

reactivation of hepatitis B	
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 2: 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 Re-challenge).	• If the patient experienced a grade 1 infusion reaction, where the final infusion rate was ≥100 mg/hour, re-challenge with a rate starting at 100 mg/hour. The rate of infusion can be escalated in increments of 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. • If the patient experienced a Grade 2 or 3 infusion reaction, re-challenge with a rate starting at 50 mg/hour. The rate of infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. *If a grade 3 IR recurs for the 2nd time, discontinue permanently (do not re-challenge).
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.	
4	• Stop the infusion.	• Discontinue permanently (do not

	• Aggressively manage symptoms.	re-challenge).

Hepatic Impairment

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

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. NHL patients ≥ 65 years of age experienced more serious adverse effects than younger patients. No efficacy differences were observed between older and younger patients.

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F - Adverse Effects

Refer to oBINutuzumab drug monograph(s) for additional details of adverse effects

Very common (≥	Common (25-49%)	Less	Uncommon (< 10%),

50%)		common (10-24%)	but may be severe or life-threatening
• Infusion-related reaction (may be severe; immediate or delayed)	• Increased LFTs (may be severe) • Myelosuppression +/- infection (including atypical, viral reactivation), bleeding (may be severe) • Increased creatinine (may be severe)	• Cough, dyspnea • Fever	• Arterial / venous thromboembolism • Arrhythmia • Tumour lysis syndrome • Secondary malignancy • Hemolysis • Capillary leak syndrome • Pancreatitis • Pneumonitis • PML • GI perforation • Anaphylaxis, serum sickness

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G - Interactions

Refer to oBINutuzumab drug monograph(s) for additional details

- No clinical drug interaction studies have been conducted with obinutuzumab.
- Consider withholding antihypertensives (if applicable) 12 hours prior to obintuzumab infusion, during infusion and for the first hour after drug administration, and withholding concomitant medications that increase bleeding risk, especially in the first cycle.
- Use with caution and monitor closely for infections when given with other immunosuppressive drugs.

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H - Drug Administration and Special Precautions

Refer to oBINutuzumab drug monograph(s) for additional details

Administration

- 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.
- 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

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

Contraindications

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

Precautions

- Obinutuzumab should not be given to patients with 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.

Pregnancy/Lactation:

- 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.
- Breastfeeding is not recommended during treatment and for at least 18 months after the last

dose.

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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

- CBC; Baseline, before each dose and as clinically indicated following treatment completion
- Liver and renal function tests, electrolytes; Baseline and prior to each cycle
- 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 for several months after the last infusion.
- Cardiac tests for all patients with cardiac risk factors; Baseline and as clinically indicated
- Infusion-related reactions; During and after each infusion
- Clinical toxicity assessment for tumour lysis syndrome, hypersensitivity, infection, bleeding, thromboembolism, neurologic, respiratory, 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 - Administrative Information

Approximate Patient Visit	3 hours
Pharmacy Workload (average time per visit)	18.249 minutes
Nursing Workload (average time per visit)	74.833 minutes

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K - References

Obinutuzumab drug monograph, Cancer Care Ontario.

Cheson BD, Chua N, Mayer J, et al. Overall survival benefit in patients with rituximab-refractory indolent non-Hodgkin lymphoma who received obinutuzumab plus bendamustine induction and obinutuzumab maintenance in the GADOLIN study. J Clin Oncol. 2018 Aug 1;36(22):2259-66.

December 2019 Updated infusion reaction information in Dose Modifications and Drug Administration and Special Precautions sections.

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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