Regimen Monograph

A - Regimen Name

CVP+OBIN Regimen

Cyclophosphamide-vinCRIStine-Prednisone-oBINnutzumab

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	For the treatment of patients with follicular lymphoma† whose disease is refractory* to a rituximab-containing regimen and has a good performance status † indolent lymphoma histologies other than follicular lymphoma (excluding CLL and mantle cell lymphoma) may be eligible for obinutuzumab funding (refer to NDFP form) * no response to OR progression during or within 6 months after rituximab or a rituximab-containing regimen
Supplementary Public Funding	**oBINutuzumab** New Drug Funding Program (Obinutuzumab - In Combination with Chemotherapy for Refractory Follicular Lymphoma)

prednisone
ODB - General Benefit (prednisone)

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B - Drug Regimen

CVP+OBIN (induction)

Cycle 1:

oBINutuzumab	1000 mg	IV	Days 1, 8 and 15
prednisone†	100 mg	PO	Daily on Days 1 to 5

(†On Day 1 to be given as part of premedication before oBINutuzumab)

vinCRIStine	1.4 mg /m²	IV (maximum 2 mg)	Day 1
cyclophosphamide	750 mg /m²	IV	Day 1

Cycles 2 to 6:

oBINutuzumab	1000 mg	IV	Day 1
prednisone†	100 mg	PO	Daily on Days 1 to 5

(†On Day 1 to be given as part of premedication before oBINutuzumab)

vinCRIStine	1.4 mg /m²	IV (maximum 2 mg)	Day 1
cyclophosphamide	750 mg /m²	IV	Day 1

For obinutuzumab maintenance use, report as regimen OBIN(MNT) after CVP+OBIN induction.

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C - Cycle Frequency

Induction: REPEAT EVERY 21 DAYS for up to 6 cycles, unless disease progression or unacceptable toxicity (see NDFP form)

For patients who responded to or have stable disease after induction therapy, refer to maintenance obinutuzumab regimen - OBIN(MNT).

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate
Minimal (Days 8 and 15 of Cycle 1)

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Obinutuzumab:

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 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 cycle.

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

Premedication recommendations:

Treatment cycle, day	Patients	Premedication
Cycle 1, Day 1	All	IV corticosteroid*/^ completed at least 1 hr prior to infusion & PO analgesic/antipyretic** & antihistamine*** at least 30 min prior to infusion

Subsequent infusions	Patients with no prior IR during previous infusion	PO analgesic/antipyretic** at least 30 min prior to infusion
	Patients with grade 1 or 2 IR with previous infusion	PO analgesic/antipyretic** & 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*/^ completed at least 1 hr prior to infusion & PO analgesic/antipyretic** & antihistamine*** at least 30 min prior to infusion

*e.g. 100 mg prednisone or 20 mg dexamethasone. Hydrocortisone should not be used as it has not been effective in reducing IR rates.

^ 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.

**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. The following recommendations have been adapted from clinical trials or product monographs and may be considered.

Dosage with toxicity

No dose reductions are recommended for obinutuzumab. The infusion may be discontinued, held or its rate reduced as described in the table below.

Toxicity	Obinutuzumab dose*, **	Vincristine (% previous dose)*,**	Cyclophosphamide (% previous dose)*,**
Grade 4 hematologic toxicity, febrile neutropenia or thrombocytopenic bleeding	Hold until ≤ grade 2, restart at usual dose. Discontinue if no recovery within 4 weeks.	No change	75% or GCSF for low ANC Discontinue if no recovery within 4 weeks
Grade 2 or 3 related organ/non-hematologic toxicity	Hold until ≤grade 1. Discontinue if no recovery within 4 weeks	100%	Grade 3: 75%
Neurotoxicity	100%	***Mild***: 67%; ***Moderate***: Hold until recovery, then ↓ 50%; ***Severe****:* Discontinue	100%
Cystitis	100%	100%	Hold until resolved
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. Discontinue if confirmed.		

*Missed doses may be administered later at physician discretion; the q28 day interval should be maintained.
**Hold up to 4 weeks. Before retreatment, major organ toxicities should recover to ≤ grade 1 (or as specified in table above), platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x 10^9/L.

Obinutuzumab Infusion Reactions:

Toxicity Grade	Obintuzumab dose
Grade 1-2 Infusion Reaction (IR)	Reduce infusion rate and treat symptoms. Restart once resolved. Escalate infusion rate as tolerated at increments appropriate for treatment dose (see table in Drug Administration section).
Grade 3 IR	Hold infusion and treat symptoms. Restart once resolved at no more than half the previous rate. Escalate infusion rate as tolerated at increments appropriate for treatment dose (see table in Drug Administration section).
Grade 4 IR, 2nd episode of grade 3 IR (during same or subsequent infusion), acute life-threatening respiratory symptoms or Anaphylaxis / serum sickness	Discontinue

Hepatic Impairment

For **obinutuzumab**, safety and efficacy have not been established in patients with hepatic impairment.

Consider dose modification for **vincristine** for severe increase in LFTs.

(Continued on next page)

Bilirubin	Vincristine (% previous dose)	Cyclophosphamide (% previous dose)	Obinutuzumab
1 – 2 X ULN	50%	100%	No data
2 – 4 x ULN	25%	Caution	
> 4 ULN	OMIT	Caution	

Renal Impairment

For **obinutuzumab**, patients who have a creatinine clearance < 50 mL/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	Cyclophosphamide dose	Vincristine dose
> 50	No dose adjustment	100%	No dose adjustment required
30-50	No dose adjustment; use with caution	75%	
10-29	No data		
<10		Use with extreme caution or discontinue	

Dosage in the Elderly

No dose adjustment is required. Patients ≥ 65 years experienced more serious adverse events than younger patients. No efficacy differences were observed between older and younger patients.

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F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Nausea, vomiting • Infusion-related reaction (immediate or delayed; may be severe)	• Myelosuppression +/- infection (including atypical, viral reactivation), bleeding (may be severe • Increased LFTs (may be severe) • Increased creatinine (may be severe)	• Fatigue • Flu-like symptoms • Constipation • Diarrhea • Abdominal pain • Anorexia • Rash (may be severe) • Musculoskeletal pain • Headache • Insomnia • Alopecia • Cough, dyspnea • Steroid effects • Peripheral neuropathy • Mucositis • Cystitis • Fever	• Arterial / venous thromboembolism • Cardiotoxicity • Arrhythmia • QT prolongation • GI perforation • Tumour lysis syndrome • Secondary malignancy • SIADH • Autonomic or cranial neuropathy • PML • Hemolysis • Capillary leak syndrome • Pancreatitis • Pneumonitis • VOD • Anaphylaxis, serum sickness

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G - Interactions

Refer to oBINutuzumab, vinCRIStine, cyclophosphamide 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.
- Caution and monitor closely for infections when given with other immunosuppressive drugs.
- Caution with use of CYP3A4 inhibitors and cyclophosphamide; avoid grapefruit for 48 hours

before and on day of cyclophosphamide
- Avoid combination of vincristine and verapamil or nifedipine; monitor closely if given concurrently
- Monitor serum phenytoin levels when used with vincristine, and adjust phenytoin dose prn

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H - Drug Administration and Special Precautions

Refer to oBINutuzumab, vinCRIStine, cyclophosphamide drug monograph(s) for additional details

Administration:

obinutuzumab

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 2-6, day 1	1000 mg	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 grade 2 or 3 IR. May escalate as tolerated by 50 mg/hr q30 min to max of 400 mg/hr.

*For infusion rate modifications in the case of IR, see dosage with toxicity section

- 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

vinCRIStine

FOR INTRAVENOUS USE ONLY. Vincristine is lethal if given intrathecally. No successful antidotes have been described. **Syringes containing this product should be labelled "WARNING – FOR INTRAVENOUS USE ONLY. FATAL if given by other routes."**

- Direct IV push not recommended, due to risk of inadvertent intrathecal administration.
- For intermittent IV use, may mix in small volume minibag (ie. 50mL NS or D5W for adults).
- Infuse IV via gravity. Infusion pumps should not be used peripherally, since they deliver infusions at higher pressures and may continue to infuse when extravasation occurs.
- During the infusion, suggest nurse to remain present with the patient to observe the IV site for extravasation.

cyclophosphamide

- Oral hydration is strongly encouraged; for PO cyclophosphamide: 8-10 (8oz) glasses of fluid per day; for IV cyclophosphamide: 2-3 L of fluid/day; poorly hydrated patients may need more IV hydration. Inadequate total hydration may result in dose-related hemorrhagic cystitis. Patients should be encouraged to empty their bladder frequently to minimize dwell times.
- Dilute in 250mL NS and infuse over 30 minutes.
- Use sodium chloride 0.9% to reconstitute cyclophosphamide
- Do not reconstitute or dilute with benzyl alcohol-containing solutions (ie. Bacteriostatic sodium chloride), since it may catalyse the decomposition of cyclophosphamide or cause toxicity in infants
- Avoid the use of aluminium-containing preparation and administration equipment, since darkening of aluminium and gas production have been reported.

Contraindications

- Patients who have a hypersensitivity to this obinutuzumab, vincristine or other vinca alkaloids, cyclophosphamide, prednisone or any of its components.
- Patients with the demyelinating form of Charcot-Marie-Tooth Syndrome or childhood polio
- Vincristine intrathecal administration is **absolutely contraindicated**.
- (cyclophsphamide) patients with urinary outflow obstruction
- (cyclophosphamide) patients with adrenal insufficiency
- (cyclophosphamide) in combination with neuromuscular blockers

Precautions

- Do not give to patients who have an active infection.
- Use with extreme caution in patients who are positive for hepatitis.
- Avoid live and live-attenuated vaccines during treatment and until B-cell recovery. Following vaccination, do not start obinutuzumab until protective antibody titres have been reached.
- Reduced immunogenicity may occur with use of inactivated vaccines.
- 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 obinutuzumab 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 with obinutuzumab.
- Vincristine should not be given to patients who are receiving radiation that includes liver portals.
- Use vincristine with caution with other neuromuscular disorders, neurotoxic/ototoxic drugs, in leukopenia, complicating infection, or and in patients with Guillain-Barre Syndrome.

Pregnancy/lactation

- CVP+OBIN 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.
- Fertility may be affected.

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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 visit and as clinically indicated following treatment completion
- Liver function tests; Baseline and at each cycle
- Renal function tests and electrolytes; Baseline and at 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 tumour lysis syndrome, infection, bleeding, injection site reactions, thromboembolism, GI, hypersensitivity, neurotoxicity, cystitis, skin, pulmonary and cardiac symptoms; 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	4 hours
Pharmacy Workload (average time per visit)	37.887 minutes
Nursing Workload (average time per visit)	84.833 minutes

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K - References

Obinutuzumab, vincristine, cyclophosphamide drug monographs, 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.

Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 2017;377(14):1331-44.

Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood. 2013 Aug 15;122(7):1137-43.

May 2019 Updated emetic risk category

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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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