Obinutuzumab cycloPHOSphamide vinCRIStine and prednisoLONE (O-CVP) Therapy – 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE reimbursement status
Obinutuzumab in combination with CVP chemotherapy is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.	C82	00550a	Obinutuzumab – ODMS 01/05/2019 cycloPHOSphamide, vinCRIStine – N/A

*For post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

- Treatment is administered every 21 days for a maximum of 8 cycles or until disease progression or unacceptable toxicity develops.
    - Obinutuzumab is administered at a dose of 1000mg in combination with CVP on Day 1, 8 and Day 15 of the first 21 day treatment cycle.
    - For cycles 2-8 obinutuzumab is administered at a dose of 1000mg on day one of each 21 day treatment cycle.
- Patients who respond to induction treatment should continue to receive obinutuzumab 1000 mg as single agent maintenance therapy once every 2 months for two years or until disease progression (whichever occurs first) (**Reference NCCP regimen 00425 Obinutuzumab Maintenance Therapy-56 days**).

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Obinutuzumab[a,b]	1000mg	IV infusion	250mL 0.9% NaCl Administer at 50 mg/hour. The rate of infusion can be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.	1
1	vinCRIStine[c]	1.4mg/m^2 (Max 2mg)	IV infusion	50mL minibag 0.9% NaCl over 15 minutes	1-8
1	cycloPHOSphamide[d]	750mg/m^2	IV infusion	250mL 0.9% NaCl over 30 minutes	1-8
1, 2,3,4, 5	prednisoLONE	[e]100mg	PO		1-8
8 and 15	Obinutuzumab[a,b]	1000mg	IV infusion	[f,g] 250mL 0.9% NaCl at a maximum rate of 400mg/hour	1
1	Obinutuzumab[a,b]	1000mg	IV infusion	[f,g] 250mL 0.9% NaCl at a maximum rate of 400mg/hour	2-8

[a] If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for obinutuzumab should be maintained between doses.

[b] Obinutuzumab infusions should NOT be administered as an intravenous push or bolus.

[c]vinCRIStine is a neurotoxic chemotherapeutic agent.
Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer Here

[d]cycloPHOSphamide may also be administered as an IV bolus over 5-10 minutes.

[e]Alternative steroid regimens may be used at consultant discretion.

[f]If no infusion related reaction or if an IRR Grade 1 occurred during the prior infusion when the final infusion rate was 100 mg/hour or faster, infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

[g]If the patient experienced an IRR of Grade 2 or higher during the previous infusion administer at 50 mg/hour. The rate of infusion can be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- Previously untreated, CD20-positive follicular lymphoma (grade 1 to 3a) with advanced disease (stage III or IV, or stage II with bulk disease [tumour of ≥7 cm in the greatest dimension])
- ECOG 0-2
  Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to obinutuzumab, cycloPHOSphamide, vinCRIStine sulphate, prednisoLONE or any of the excipients.
- Pregnancy or lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Cardiac function if clinically indicated
- LDH, Uric acid, SPEP
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV*
  *See Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile and LDH prior to each cycle
- Evaluate for peripheral neuropathy prior to each cycle
- Diabetic patients should increase frequency of monitoring of blood glucose whilst taking high dose steroids
- Cardiac function as clinically indicated

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- No dose reductions of obinutuzumab are recommended
- Consider vinCRIStine dose reduction in elderly patients

Haematological:

Table 1: Recommended Dose modification in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
< 1	and/or	< 75	Delay treatment until recovery. Consider adding G-CSF.

Renal and Hepatic Impairment:

Table 2: Recommended [a-c] dose modification in renal and hepatic Impairment:

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="2">Hepatic impairment</th></tr>
<tr><td>Obinutuzumab[a]</td><td colspan="2">No dose adjustment is needed.

Haemodialysis: No need for dose adjustment is expected.</td><td colspan="2">No need for dose adjustment is expected.</td></tr>
<tr><td rowspan="5">cycloPHOSphamide[b]</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="2" rowspan="5">Mild and moderate: no need for dose adjustment is expected.

Severe: not recommended, due to risk of reduced efficacy.</td></tr>
<tr><td>≥ 30</td><td>No dose adjustment is needed</td></tr>
<tr><td>10-29</td><td>Consider 75% of the original dose</td></tr>
<tr><td><10</td><td>Not recommended, if unavoidable consider 50% of the original dose</td></tr>
<tr><td>Haemodialysis</td><td>Not recommended, if unavoidable consider 50% of the original dose</td></tr>
<tr><td>vinCRIStine[c]</td><td colspan="2">No need for dose adjustment is expected.

Haemodialysis: No need for dose adjustment is expected.</td><td>Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td colspan="3"></td><td>>51</td><td>50% of original dose</td></tr>
<tr><td colspan="5">[a-c] Renal and hepatic dose modifications from Giraud et al 2023</td></tr>
</table>

Management of adverse events:

Table 3: Recommended dose modification schedule of obinutuzumab based on adverse events

Adverse reactions	Recommended dose modification
Infusion Related Reactions (IRR) **Grade 1-2**	Reduce infusion rate. Treat symptoms.
Symptom resolution	Infusion can be continued upon resolution of symptoms and If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose.
Grade 3 • First occurrence	Temporarily stop the infusion. Treat the symptoms.
○ Symptom resolution	Upon resolution of symptoms restart infusion at no more than half the previous rate and, if the patient does not experience any IRR symptoms the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose.
• Second occurrence	Stop infusion and discontinue treatment. Stop infusion and discontinue treatment.
Grade 4	
PML	Discontinue treatment
Hypersensitivity reaction	Discontinue treatment

Table 4: Recommended dose modification of vinCRIStine based on neurotoxicity

Symptom	Dose of vinCRIStine
Grade 1	100%
Grade 2	Hold until recovery then reduce dose by 50%
Grade 3 and 4	Omit

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here

Obinutuzumab: Minimal **(Refer to local policy)**
cycloPHOSphamide: Moderate **(Refer to local policy)**
vinCRIStine: Minimal **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS:

Table 5 describes the recommended pre-medication to be administered before obinutuzumab infusion to reduce the risk of infusion related reactions (IRRs).

Table 5: Premedication to be administered before obinutuzumab infusion to reduce the risk of IRRs

Day of treatment cycle	Patients requiring premedication	Premedication	Administration
Cycle 1: Day 1	All patients	[a,d]Intravenous corticosteroid (recommended)	Completed at least 1 hour prior to obinutuzumab infusion
		[b]Oral anti-pyretic	At least 30 minutes before obinutuzumab infusion
		[c]Anti-histamine	
All subsequent infusions	Patients with no IRR during the previous infusion	[b]Oral anti-pyretic	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1 or 2) with the previous infusion	[b]Oral anti-pyretic [c]Anti-histamine	
	Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x 10^9/L prior to next treatment	[a,d]Intravenous corticosteroid	Completed at least 1 hour prior to obinutuzumab infusion
		[b]Oral anti-pyretic [c]Anti-histamine[3]	At least 30 minutes before obinutuzumab infusion

[a] *100 mg predniSONE/prednisoLONE or 20 mg dexAMETHasone or 80 mg methylPREDNISolone* ***Hydrocortisone should not be used as it has not been effective in reducing rates of IRR***.

[b] e.g. *1000 mg paracetamol*

[c] e.g. *10mg chlorpheramine*

[d] If a corticosteroid-containing chemotherapy regimen is administered on the same day as obinutuzumab, the corticosteroid can be administered as an oral medication if given at least 60 minutes prior to obinutuzumab, in which case additional IV corticosteroid as premedication is not required.

OTHER SUPPORTIVE CARE:

- G-CSF prophylaxis may be required **(Refer to local policy)**
- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRIStine)**(Refer to local policy)**
- Mouth care **(Refer to local policy)**
- Proton-pump inhibitor **(Refer to local policy)**
- Prophylactic regimen against vinCRIStine-induced constipation is recommended **(Refer to local policy)**
- Patients should have an increased fluid intake of 2-3 litres on day 1 and 2 to prevent haemorrhagic cystitis associated with cycloPHOSphamide.

ADVERSE EFFECTS:

Please refer to the relevant Summary of Product Characteristics (SmPC).

REGIMEN SPECIFIC COMPLICATIONS:

- **Hepatitis B Reactivation**: Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. (Refer to local infectious disease policy). These patients should be considered for assessment by hepatology.
- **Tumour lysis syndrome/ IRR's:** Consider 5 to 7 days of induction steroids for patients with bulky disease.

DRUG INTERACTIONS:

Consult current drug interaction databases and relevant SmPC.

REFERENCES:

1. Marcus R et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med 2017;377:1331-44
2. Hiddemann W et al. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety. J Clin Oncol 2018; 36: 2395-2404
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Obinutuzumab (Gazyvaro®) 1000 mg concentrate for solution for infusion Summary of Product Characteristics. Accessed January 2024. Last updated November 2023 . Available at: https://www.ema.europa.eu/en/documents/product-information/gazyvaro-epar-product-information_en.pdf
6. vinCRIStine Sulphate 1 mg/ml Solution for Injection or Infusion Summary of Product Characteristics. Accessed January 2024. Last updated October 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-232-001_09102023163547.pdf
7. cycloPHOSphamide (Endoxana®) 500 mg Powder for Solution for Injection or Infusion Summary of Product Characteristics. Accessed January 2024. Last updated October 2022.Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-001_21122018112107.pdf

Version	Date	Amendment	Approved By
1	26/04/19		Dr Brian Bird
2	23/07/2024	Reviewed. Updated order of administration. Updated exclusions-pregnancy and lactation. Updated renal and hepatic recommendations in line with Giraud et al. Updated and supportive care section. Added induction phase steroids for bulky disease to Regimen	Dr Brian Bird

		Specific Complications.Updated in line with NCCP standardisation.	

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.