# Obinutuzumab Cyclophosphamide VinCRIStine and Prednisolone (O- CVP) Therapy– 21 days

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | *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 – Hospital |

**If the reimbursement status is not defined [i], the indication has yet to be assessed through the formal HSE reimbursement process.*

## 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 1,000mg on day one of each 21 day treatment cycle
- Patients who respond to induction treatment should continue to receive obinutuzumab 1,000 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 the chemotherapy is administered.

| Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|
| 1 | Obinutuzumab[1,2] | 1000mg | IV infusion | 250ml 0.9% NaCl<br>Administer at 50 mg/hr.<br>The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. | 1 |
| 1 | Cyclophosphamide | 750mg/m$^2$ | IV infusion[3] | 250 ml 0.9% NaCl over 30 minutes | 1-8 |
| 1 | VinCRIStine[4] | 1.4mg/m$^2$ (Max 2mg) | IV infusion | 50ml minibag 0.9% NaCl over 15minutes | 1-8 |
| 1, 2,3, 4, 5 | Prednisolone | 100mg[5] | PO | | 1-8 |
| 8 and 15 | Obinutuzumab[1,2] | 1000mg | IV infusion[2] | 250ml 0.9% NaCl at a maximum rate of 400mg/hr[,6,7] | 1 |
| 1 | Obinutuzumab[1,2] | 1000mg | IV infusion[2] | 250ml 0.9% NaCl at a maximum rate of 400mg/hr[6,7] | 2-8 |

[1] 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

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

[3]Cyclophosphamide may also be administered as an IV bolus over 5-10mins

[4]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

[5]Alternative steroid regimens may be used at consultant discretion

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

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

## ELIGIBILTY:

- 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 [tumor of ≥7 cm in the greatest dimension])
- ECOG 0-2
- Adequate haematological, renal and liver status

## EXCLUSIONS:

- Hypersensitivity to obintuzumab, cyclophosphamide, vinCRIStine sulphate, prednisolone or any of the excipients.

## 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 Adverse Effects/Regimen Specific Complications

**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 obinutzumab 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 Dose modification in Renal and Hepatic Impairment:**

| Drug | Renal impairment | | Hepatic impairment | | | |
|---|---|---|---|---|---|---|
| **Obinutuzumab** | **CrCl (ml/min)** | **Dose** | Safety and efficacy not established in patients with impaired hepatic function. No specific dose recommendations can be made. | | | |
| | 30-89 | 100% | | | | |
| | <30 | Safety and efficacy not established | | | | |
| **Cyclophosphamide** | **CrCl (ml/min)** | **Dose** | Dose reduction may need to be considered in severe hepatic impairment. Clinical Decision | | | |
| | >20 | 100% | | | | |
| | 10-20 | 75% | | | | |
| | <10 | 50% | | | | |
| **VinCRIStine** | No dose reduction required | | **Bilirubin (micromol/L)** | | **AST/ALT** | **Dose** |
| | | | 26-51 | or | 60-180 | 50% |
| | | | >51 | and | Normal | 50% |
| | | | >51 | and | >180 | Omit |

**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)<br>**Grade 1-2**<br><br>Symptom resolution<br><br><br>**Grade 3**<br>• First occurrence<br>○ Symptom resolution<br><br><br><br>• Second occurrence<br>**Grade 4** | <br>Reduce infusion rate. Treat symptoms<br><br>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.<br><br>Temporarily stop the infusion. Treat the symptoms<br>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.<br><br>Stop infusion and discontinue treatment.<br>Stop infusion and discontinue treatment. |
| **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:** Moderate. **(Refer to local policy).**

## PREMEDICATIONS:

**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 | Intravenous corticosteroid[1,4] (recommended) | Completed at least 1 hour prior to obinutuzumab infusion |
| | | Oral anti-pyretic[2] | At least 30 minutes before obinutuzumab infusion |
| | | Anti-histamine [3] | |
| **All subsequent infusions** | Patients with no IRR during the previous infusion | Oral anti-pyretic[2] | At least 30 minutes before obinutuzumab infusion |
| | Patients with an IRR (Grade 1 or 2) with the previous infusion | Oral anti-pyretic[2] Anti-histamine[3] | |
| | Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x $10^9$/L prior to next treatment | Intravenous corticosteroid[1,4] | Completed at least 1 hour prior to obinutuzumab infusion |
| | | Oral anti-pyretic[3] Anti-histamine | At least 30 minutes before obinutuzumab infusion |

[1] *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***.
[2] e.g. *1,000 mg paracetamol*
[3] e.g. *10mg chlorpheniramine*
[4] .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,
- 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**).**

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

*The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details*.

**Obinutuzumab is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.**

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.

**Obinutuzumab**

- **Infusion Related Reactions**: Most reactions are mild or moderate and are further reduced by slowing or temporarily stopping the infusion. Risks for IRRs include high tumour burden, renal impairment and Cumulative Illness Rating Scale (CIRS) >6. If the patient experiences an IRR, the infusion should be managed according to the grade of the reaction (see Table 2).
- **Hypotension**, as a symptom of IRRs, may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration
- **Tumour lysis syndrome**: There is an increased risk with high tumour burden or a high circulating lymphocyte count >25x$10^9$/L
- **Neutropenia:** Severe and life threatening neutropenia including febrile neutropenia has been reported during treatment with obinutuzumab. Consider G-CSF, if severe and associated with infection; consider anti-microbial prophylaxis if severe and prolonged (>1 week), including anti-viral and anti-fungal prophylaxis. Cases of late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia.
- **Thrombocytopenia**: This can be severe and life-threatening, including acute onset within 24 hours post infusion; monitor closely and treat bleeding according to local policy. Renal impairment increases risk of thrombocytopenia. Dose delays may be required. Use of all concomitant therapies that could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.
- **Worsening of pre-existing cardiac conditions**: Atrial fibrillation, angina, acute coronary syndrome, myocardial infarction, hypertension and heart failure can occur in patients with underlying cardiac disease. Monitor closely and hydrate cautiously to prevent fluid overload.
- **Infections**: Do not administer if active infection; fatal infections may occur. Caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections. Risk is increased if CIRS > 6 or renal impairment present.
- **Progressive multifocal leucoencephalopathy (PML)**: New or worsening neurological, cognitive or behavioural symptoms or signs due to PML have occurred with obinutuzumab.
- **Hepatitis B Reactivation**: This can occur, causing fulminant hepatitis, hepatic failure and death. All lymphoma patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with regular liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.

**VinCRIStine**

- **Neuropathy:** VinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function,

dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months. A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.

- **Extravasation**: VinCRIStine causes pain if extravasated. **(Refer to local policy).**

## Drug interactions:

- No interaction studies have been performed with obinutuzumab.
- Vaccinations with live organism vaccines are not recommended with obinutuzumab
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

| | | |
|---|---|---|
| Obinutuzumab | - | L01XC15 |
| Cyclophosphamide | - | L01AA01 |
| VinCRIStine | - | L01CA02 |

## REFERENCES:


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- Dosage Adjustment for Cytotoxics in Renal Impairment. North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment- dosage-adjustment-for-cytotoxics.pdf
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- Vincristine Sulphate 1 mg/ml Solution for Injection or Infusion SmPC accessed Dec 2018. Available at https://www.medicines.org.uk/emc/product/1502/smpc
- Endoxana® Cyclophosphamide 500 mg Powder for Solution for Injection or Infusion SmPC accessed March 2019. Available at https://www.medicines.org.uk/emc/product/3526/smpc
- Gazyvaro 1,000 mg concentrate for solution for infusion (obinutuzumab) SmPC accessed March 2019. Available at https://www.medicines.org.uk/emc/product/3279/smpc


| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 26/04/19 | | Dr Brian Bird |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System

CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/