# Obinutuzumab Maintenance Therapy -56 day

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | *Reimbursement Status |
|---|---|---|---|
| Obinutuzumab maintenance therapy is indicated in patients with follicular lymphoma (FL) who have responded to induction treatment with obinutuzumab and chemotherapy (CHOP, CVP or bendamustine) or have stable disease | C82 | 00425a | ODMS 1/11/17 |

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

**NOTE: This regimen follows Obinutuzumab and Bendamustine Therapy-28 day (NCCP Regimen 00424) obinutuzumab and CHOP therapy (NCCP regimen 00549) or obinutuzumab and CVP therapy (NCCP regimen number 00500)**

## TREATMENT:

Obinutuzumab is administered at a dose of 1,000mg once every 2 months for two years or until disease progression

*Facilities to treat anaphylaxis MUST be present when obinutuzumab is administered.*

| Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|
| 1 | Obinutuzumab[1,2] | 1000mg | IV infusion | 250ml 0.9% NaCl<br>Administer at 50mg/hr<br>The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr[3,4] | Repeat every 2 months |

[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]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.

[4]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:

- Indication as above
- ECOG 0-2 (ECOG 3 at the discretion of the treating clinician)
- Adequate haematological, renal and liver status

## EXCLUSIONS:

- Hypersensitivity to obinutuzumab, or any of the excipients

## PRESCRIPTIVE AUTHORITY:

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

## TESTS:

**Baseline tests:**

- FBC, renal and liver profile
- LDH,
- Virology screen -Hepatitis B (HBsAg, HBcoreAb)
  *(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)

**Regular tests**:

- FBC, renal and liver profile and LDH prior to each cycle

**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.
- A dose delay of up to 4 weeks is permitted for obinutuzumab to allow recovery of hematologic toxicities to ≤grade 2 or non-haematologic toxicities to grade 1 or baseline level
- If the toxicity resolves within the 4-week period, dosing should resume
- If toxicity does not resolve, treatment should be discontinued
- No dose adjustment is required in elderly patients

**Renal and Hepatic Impairment:**

**Table 1: 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 | |

**Table 2: Dose modification schedule based on adverse events**

| Adverse reactions | Recommended dose modification |
|---|---|
| **Infusion Related Reactions** (IRR)<br>**Grade 1-2**<br><br>Symptom resolution<br><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 |

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

Obinutuzumab: Minimal **(Refer to local policy).**

### PREMEDICATIONS:

Table 3 describes the recommended premedication to be administered before obinutuzumab infusion to reduce the risk of infusion related reactions (IRRs)**.**

**Table 3: Premedication to be administered before obinutuzumab infusion to reduce the risk of IRRs**

| Day of treatment cycle | Patients requiring premedication | Premedication | Administration |
|---|---|---|---|
| **All infusions in maintenance phase** | 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]<br>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] | Completed at least 1 hour prior to obinutuzumab infusion |
| | | Oral anti-pyretic[3]<br>Anti-histamine | At least 30 minutes before obinutuzumab infusion |

[1] *100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone* ***Hydrocortisone should <u>not</u> 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*

**OTHER SUPPORTIVE CARE**: Not required in maintenance

## 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.**

**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
- **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**: All 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, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent 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.

## DRUG INTERACTIONS:

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

## ATC CODE:

Obinutuzumab L01XC15

## REFERENCES:

1. Sehn, Laurie H et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. The Lancet Oncology , 2016;V 17 ( 8) , 1081 - 1093

2. Gazyvaro Summary of Product Characteristics Accessed May 2019 Available at: https://www.medicines.org.uk/emc/product/3279/smpc#POSOLOGY
3. Marcus R et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med 2017;377:1331-44.
4. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002799/WC500171594.pdfFriedberg JW Progress in Advanced Stage Follicular Lymphoma J Clin Oncol 2018 http://ascopubs.org/doi/full/10.1200/JCO.2018.79.3083
5. 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 http://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.8960

| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 10/10/2017 | | Prof Elisabeth Vandenberghe |
| 2 | 26/07/2019 | Updated regimen title and indication. Updated information on IRR infusion rate escalation management as per SmPC update Amended recommendation for Hep B reactivation | Prof Elisabeth Vandenberghe |

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/