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 01/11/17

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 00550)

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]	1000mg	IV infusion	250ml 0.9% NaCl Administer at 50mg/hr The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr[2, 3]	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]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.					
[3]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.					

ELIGIBILITY:

- 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), Hepatitis C and HIV.
  *(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 haematologic 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) **Grade 1-2** Symptom resolution **Grade 3** • First occurrence ○ Symptom resolution • Second occurrence **Grade 4**	 Reduce infusion rate. Treat symptoms 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. Temporarily stop the infusion. Treat the symptoms 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. Stop infusion and discontinue treatment. 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[1]	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1 or 2) with the previous infusion	Oral anti-pyretic[1] Anti-histamine[2]	
	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[3]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral anti-pyretic[1] Anti-histamine[2]	At least 30 minutes before obinutuzumab infusion

[1]e.g. 1000 mg paracetamol
[2]e.g. 10mg chlorphenamine
[3]100mg prednisone/prednisolone or 20mg dexamethasone or 80mg methylprednisolone. **Hydrocortisone should not be used as it has not been effective in reducing rates of IRR**.

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

- **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, hypotension 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 and/or a high circulating lymphocyte count (>25x109/L) and/or renal impairment (CrCl < 70ml/min).
- **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. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of thrombocytopenia.

- **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**: 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.

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.

REFERENCES:

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2. Marcus R et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med 2017;377:1331-44.
3. Friedberg JW. Progress in Advanced Stage Follicular Lymphoma. J Clin Oncol 2018 http://ascopubs.org/doi/full/10.1200/JCO.2018.79.3083
4. 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 Aug 10;36(23):2395-2404. doi: 10.1200/JCO.2017.76.8960. Epub 2018 Jun 1. PMID: 29856692.
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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
3	26/06/2022	Reviewed. Added to baseline tests. Amended adverse effects – tumour lysis syndrome, neutropenia, thrombocytopenia and hepatitis B reactivation.	Prof Elisabeth Vandenberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.