Obinutuzumab and Bendamustine Therapy – 28 day cycle

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Obinutuzumab in combination with bendamustine is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.	C82	00424a	ODMS 1/11/17
Obinutuzumab in combination with bendamustine is indicated for the treatment of patients with previously untreated advanced follicular lymphoma	C82	00424b	ODMS 01/05/19

**If a reimbursement indicator 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 consists of 6 x 28 day cycles of obinutuzumab and bendamustine as follows unless disease progression or unacceptable toxicity occurs.
  - Obinutuzumab is administered at a dose of 1000mg on Day 1, 8 and Day 15 of the first 28 day treatment cycle. Bendamustine is administered on Day 1 and Day 2 of each 28 day cycle.
  - For cycles 2-6 obinutuzumab is administered at a dose of 1,000mg on Day 1 of every 28 day treatment cycle. Bendamustine is administered on Day 1 and Day 2 of each 28 day cycle.
- First Line : Patients who achieve a complete or partial response to induction treatment with obinutuzumab in combination with bendamustine should continue to receive obinutuzumab 1,000 mg as single agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first) Reference NCCP Protocol 00425 Obinutuzumab Maintenance Therapy-2monthly)
- Second Line :Patients who respond to induction treatment (i.e. the initial 6 treatment cycles) with obinutuzumab in combination with bendamustine or have stable disease 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 Protocol 00425 Obinutuzumab Maintenance Therapy-2monthly)

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

Order of admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Obinutuzumab	1000mg	IV infusion	250ml 0.9% NaCl 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.	1
2	1	Bendamustine	90mg/m^2	IV infusion	250 to 500 mL 0.9% NaCl over 1 hour	1
1	2	Bendamustine	90mg/m^2	IV infusion	250 to 500 mL 0.9% NaCl over 1 hour	1
1	8 and 15	Obinutuzumab	1000mg	IV infusion	250ml 0.9% NaCl*	1
1	1	Obinutuzumab	1000mg	IV infusion	250ml 0.9% NaCl*	2-6
2	1 and 2	Bendamustine	90mg/m^2	IV infusion	250 to 500 mL 0.9% NaCl over 1 hour	2-6
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						
Obinutuzumab infusions should NOT be administered as an intravenous push or bolus.						
*If no infusion related reaction 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. 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:

1L treatment

- 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 status 0-2
- Adequate haematological, renal and liver status

2 L treatment

- CD20-positive indolent non-Hodgkin lymphoma refractory to riTUXimab as outlined above
- ECOG 0-2 (ECOG 3 at the discretion of the treating clinician)

EXCLUSIONS:

- Hypersensitivity to obintuzumab, bendamustine or to 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, U&E, LFTs,
- LDH, Uric acid
- ECG(+/- echocardiogram as clinically indicated)
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV.

*See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, U&E, LFTs, LDH monthly
- ECG 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.
- A dose delay of up to 4 weeks is permitted for obinutuzumab and bendamustine 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, but the bendamustine dose reduces to 60 mg/m^2 per day for subsequent cycles depending on the number of previous episodes of that toxicity.
- 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		
Bendamustine	**CrCl (ml/min)**	**Dose**	**Serum bilirubin (micromol/L)**	**Dose**
	>10	No dose adjustment necessary	< 21	No dose adjustment necessary
	Experience in patients with severe renal impairment is limited.		21-51	30% Dose reduction
			>51	No data available

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 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).
Bendamustine: Moderate (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
Cycle 1: Day 1	All patients	Intravenous corticosteroid[1] (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]	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*

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Proton pump inhibitor **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Mouth care **(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.

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 >25x10^9/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. 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:** 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 during chemotherapy and maintenance therapy and for six months afterwards (Refer to local policy). These patients should be monitored with regular liver function tests and hepatitis B virus DNA levels at least every two months. If the hepatitis B virus DNA level rises, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy

Bendamustine

- **Skin reactions:** A number of skin reactions have been reported with bendamustine therapy. These events have included rash, toxic skin reactions and bullous exanthema. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, bendamustine should be withheld or discontinued. For severe skin reactions where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued.

Refer to NCCP Protocol 00346 RiTUXimab and Bendamustine Therapy for further information on adverse reactions /Regimen Specific Complications for Bendamustine

DRUG INTERACTIONS:

- No interaction studies have been performed with obinutuzumab.
- Vaccinations with live organism vaccines are not recommended.
- Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme, Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exists.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Obinutuzumab L01XC15
Bendamustine L01AA09

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. Marcus R et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med 2017;377:1331-44.
3. 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
4. Gazyvaro Summary of Product Characteristics Accessed March 2017 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002799/WC500171594.pdf
5. Bendamustine 25mg Powder for Concentrate for Solution for Infusion Summary of Product Characteristics. Accessed March 2017Available at: http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1390-095-001_07042016161053.pdf

Version	Date	Amendment	Approved By
1	10/10/2017		Prof Elisabeth Vandenberghe
2	26/04/2019	Updated to include indication in first line therapy. Updated information on IRR infusion rate escalation management as per SmPC update	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/