Obinutuzumab and Chlorambucil Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy.	C91	00286a	Obinutuzumab- ODMS Chlorambucil -CDS

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 chlorambucil as follows unless disease progression or unacceptable toxicity occurs.

Obinutuzumab is administered at a dose of 1000mg over Day 1 and Day 2, and on Day 8 and Day 15 of the first 28 day treatment cycle. Two infusion bags should be prepared for the infusion on Days 1 and 2 (100 mg for Day 1 and 900 mg for Day 2).
If the first bag is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions and medical supervision are available throughout the infusion.
If there are any modifications of the infusion rate or interruptions during the first 100 mg the second bag must be administered the following day.

For cycles 2-6 obinutuzumab is administered at a dose of 1,000mg once every 28 days
Chlorambucil is administered orally on day 1 and 15 of each cycle.

Facilities to treat anaphylaxis MUST be present when obinutuzumab is administered

Cycle	Day	Drug	Dose	Route	Diluent & Rate
1	**1**	Chlorambucil	0.5mg/kg	PO	N/A
1	**1**	Obinutuzumab	100mg	IV infusion	100ml of 0.9% NaCl. Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
1	**2** (or Day 1 continued)	Obinutuzumab	900mg	IV infusion	250ml 0.9% NaCl. If no infusion reaction during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
1	**8**	Obinutuzumab	1000mg	IV infusion	250ml 0.9% NaCl. If no infusion reaction during the prior infusion when final infusion rate was 100mg/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.
1	**15**	Chlorambucil	0.5mg/kg	PO	N/A
1	**15**	Obinutuzumab	1000mg	IV infusion	250ml 0.9% NaCl. 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.
2-6	**1**	Obinutuzumab	1000mg	IV infusion	
2-6	**1**	Chlorambucil	0.5mg/kg	PO	N/A
2-6	**15**	Chlorambucil	0.5mg/kg	PO	N/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					
Obinutuzumab infusions should NOT be administered as an intravenous push or bolus.					
Chlorambucil tablets should be taken on an empty stomach (one hour before a meal or 3 hours after).					
Chlorambucil tablets should be stored in their original container between 2^0C and 8^0C.					

ELIGIBILTY:

- ECOG 2-4
- Life expectancy < 24 months

EXCLUSIONS:

- Hypersensitivity to obintuzumab, chlorambucil or to any of the excipients

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- Blood, renal and liver profile
- LDH and uric acid

- ECG (+/- echocardiogram as clinically indicated)
- Hepatitis B and C serology**.** All patients should be tested for both HBsAg and HBcoreAb. *See Adverse Effects/Regimen Specific Complications

Regular tests:

- Blood, renal and liver profile monthly
- LDH
- 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 chlorambucil and obinutuzumab to allow recovery of hematologic toxicities to ≤grade 2 or non-haematologic toxicities to grade 1 or baseline level
- No dose adjustment is required in elderly patients

Haematological:

Cytopenias: Dose modifications of **chlorambucil** only required if cytopenia felt to be due to treatment rather than disease as follows**:**

Table 1: Dose modifications of chlorambucil for haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose modification of chlorambucil
<1	**OR**	<75	Delay next cycle by 1 week; if the values have not changed after 2 weeks delay, reduce dose by 50%
<0.5	**OR**	<50	Delay treatment until counts rise above these levels with subsequent dose modification as above if required

Renal and Hepatic Impairment:

Table 2: Dose modification of obinutuzumab and chlorambucil in renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment
Chlorambucil	No dose reductions necessary, however, monitor patients carefully, as they are more prone to myelosuppression.		Dose reduce in patients with gross hepatic dysfunction. Modify dose according to response. Once the tolerance is established after the first month of therapy the dosage should be modified according to response e.g. level of haematological suppression.
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	

Non-haematological toxicity:

Table 3: Dose modification for adverse events

Adverse reactions	Recommended dose modification
Infusion Related Reactions (IRR) Grade 1-2	Reduce infusion rate and treat symptoms. Infusion can be continued upon symptom resolution 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 (see Treatment Table). The day 1 (cycle 1) infusion rate may be increased back up to 25mg/hr after 1 hour, but not increased further.
Grade 3 First occurrence	Temporarily stop the infusion and treat the symptoms. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) 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 (see Treatment Table). The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.
Second occurrence	Stop infusion and discontinue treatment.
Grade 4	Stop infusion and discontinue treatment.
Progressive multifocal leukoencephalopathy (PML)	Discontinue treatment
Hypersensitivity	Discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Obinatuzumab **Minimal** (Refer to local policy).
Chlorambucil **Minimal** –low (Refer to local policy).

PREMEDICATIONS:

Table 4 describes the recommended premedication to be administered before obinutuzumab infusion to reduce the risk of infusion related reactions (IRRs).

Table 4: 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	Corticosteroid PO[1]	Completed at least 12 hours pre treatment (may be of additional benefit in reducing IRRs (Ref 1))
Cycle 1: Day 1	All patients	Intravenous corticosteroid[2]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral analgesic/anti-pyretic[3]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic medicine[4]	
Cycle 1: Day2	All patients	Intravenous corticosteroid[2]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral analgesic/anti-pyretic[3]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic medicine[4]	
Cycle 1: Day 8, Day 15	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[2]	Completed at least 1 hour prior to obinutuzumab infusion
Cycles 2-6: Day 1	All patients	Oral analgesic/anti-pyretic[3]	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1 or more) with the previous infusion	Anti-histaminic medicine[4]	

[1] *20 mg dexamethasone PO or 100 mg prednisone/prednisolone*
[2] *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.
[3] e.g. *1,000 mg paracetamol*
[4] e.g. *50 mg diphenhydramine*

OTHER SUPPORTIVE CARE :

- Prophylaxis with adequate hydration and administration of uricostatics (e.g. *allopurinol*) starting 12-24 hours prior to start of therapy is recommended for patients with high circulating lymphocyte count (>25x10^9/L) to reduce the risk of tumour lysis syndrome

- 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

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Obinutuzumab is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Infusion Related Reactions:** These are minimised by administering day 1 obinutuzumab over 2 days in combination with pre-medications, as outlined in table 4. 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 3).
- **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. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.
- **Tumour lysis syndrome:** There is an increased risk with high tumour burden and/or a high circulating lymphocyte count (>25x10^9/L) and/or renal impairment (CrCl<70ml/min); minimise with TLS prophylaxis and manage TLS according to best medical practice **(Refer to local policy).**
- **Neutropenia:** Severe and life threatening neutropenia including febrile neutropenia has been reported during treatment with obinutuzumab. Patients who experience neutropenia should be closely monitored. 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 <50mL/min) are more at risk of neutropenia. Dose delays may be required.
- **Thrombocytopenia:** This can be severe and life-threatening, including acute onset within 24 hours post infusion; monitor closely and treat bleeding according to best practice. 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.
- **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 antiviral therapy, for the entire duration of chemotherapy and for six months afterwards (Refer to local policy). 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.
- **Progressive multifocal leucoencephalopathy (PML):** New or worsening neurological, cognitive or behavioural symptoms or signs due to PML have occurred with obinutuzumab.

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
Chlorambucil	L01AA02

REFERENCES:

1. A Multicenter, Open-Label, Single-Arm, Phase IIIb International Study Evaluating the safety of Obinutuzumab Alone or in combination with chemotherapy in patients with previously untreated or relapsed/refractory Chronic Lymphocytic Leukaemia Protocol Number M028543 Version 4.1, 6 May 2015.
2. Goede V et al. Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions. N Engl J Med 2014;370:1101-10
3. Goede V, Fischer K, Humphrey K, Asikanius E, Busch R, Engelke A, et al. Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase III trial. J Clin Oncol 31, 2013 (suppl; abstr 7004).
4. Obinatuzumab (Gazyvaro®) Summary of Product Characteristics EMA Last updated: 28/08/2019. Accessed September 2019 Available at: https://www.ema.europa.eu/en/documents/product-information/gazyvaro-epar-product-information_en.pdf
5. Chlorambucil (Leukeran 2mg tablets) Summary of Product Characteristics Last updated: 12/01/2018 Accessed September 2019.Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1691-007-001_12012018141037.pdf
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V1 2018. https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf

Version	Date	Amendment	Approved By
1	01/10/2015		Dr A Fortune
2	20/09/2017	Updated with new NCCP regimen template. Inclusion of Hep B and C testing in Baseline Tests. Updated emetogenic potential as per NCCN and updated adverse reactions	Dr A Fortune
3	19/11/2019	Reviewed. Updated adverse events and dose modifications non-haematological toxicity	Dr A Fortune, Hilary O'Leary

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.