Indication	First line treatment of CD20+ Chronic lymphocytic Leukaemia (CLL) in patients who are unsuitable for full dose fludarabine or bendamustine based therapy.
Treatment Intent	Disease modification
Frequency and number of cycles	Repeat every 28 days. Maximum of 6 cycles
Monitoring Parameters pre-treatment	• Virology status checked prior to cycle 1. • Monitor FBC, U&Es and LFTs Day 1 of each cycle plus Day 8 & Day 15 of cycle 1 • Monitor LDH at baseline then Day 1 of every other cycle • **Haematological toxicity:** If neutrophils < 1.0 x 10^9/L and / or platelets < 50 x 10^9/L, delay until counts have recovered, then continue with full dose treatment. • **Risk of tumour lysis syndrome:** Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 10^9/L) and/or renal impairment (CrCl <70 mL/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. *allopurinol*),starting 12-24hours prior to start of infusion • **Antihypertensives:** Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each infusion and for the first hour after administration. • **Renal impairment:** o Obinutuzumab: No dose adjustment is required if CrCl >/= 30ml/min. There is no data for CrCl < 30ml/min. o Chlorambucil: No dose adjustment required. If CrCl <50mL/min monitor closely for myelosuppression. • **Hepatic impairment:** o Obinutuzumab: No data available in impaired hepatic function. No specific dose recommendations can be made clinical decision. o Chlorambucil: Patients with hepatic impairment should be closely monitored for signs and symptoms of toxicity. Dose reduction should be considered in patients with severe hepatic impairment. • Patients with a history of cardiac disease should be monitored closely. • Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with obinutuzumab. If suspected treatment should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. • Patients should not receive live vaccines during treatment, and until B cell counts have normalised. • **<u>Obinutuzumab infusion rate notes:</u>** • Notes CYCLE 1: 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. • **<u>DAY ONE cycle 1:</u> Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.** o <u>In the event of an infusion related reaction (IRR), the administration rate should be modified as follows:</u> o Grade 1-2 IRR (mild-moderate): Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if participant does not experience any IRR symptoms, infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

	○ Grade 3 IRR (severe): Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if participant does not experience any IRR symptoms, infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. If a grade 3 IRR occurs at re-challenge, stop infusion immediately and discontinue therapy permanently. ○ Grade 4 IRR (life threatening): Stop infusion and discontinue therapy. • **DAY 2 cycle 1:** Administer at 50 mg/hr. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 50 mg per hour every 30 minutes to a maximum rate of 400 mg per hour. ○ In the event of an infusion related reaction (IRR), the administration rate should be modified as follows: ○ Grade 1-2 IRR (mild-moderate): Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. ○ Grade 3 IRR (severe): Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If a grade 3 IRR occurs at re-challenge, stop infusion immediately and discontinue therapy permanently. ○ Grade 4 IRR (life threatening): Stop infusion and discontinue therapy. • **DAY 8 and 15 cycle 1 and DAY 1 cycle 2-6:** Administer at 100 mg/hr. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 100 mg per hour every 30 minutes to a maximum rate of 400 mg per hour. ○ In the event of an infusion related reaction (IRR), the administration rate should be modified as follows: ○ Grade 1-2 IRR (mild-moderate): Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. ○ Grade 3 IRR (severe): Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If a grade 3 IRR occurs at re-challenge, stop infusion immediately and discontinue therapy permanently. ○ Grade 4 IRR (life threatening): Stop infusion and discontinue therapy.
References	KMCC proforma HAEM-CLL-026 v1 ARIA regimen CLL-026 SPC accessed online 03.11.2021 BNF accessed on line 03.11.21

NB For funding information, refer to CDF and NICE Drugs Funding List

Cycle 1

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Methylprednisolone	80mg	IV	Over 15 min	In 100ml Sodium Chloride 0.9%. Infusion **must be completed at least 1 hour prior to the obinutuzumab infusion.**
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine	10mg	IV	Slow bolus over 1min	
	Ensure adequate hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10^9/L to reduce the risk of TLS.				
	OBINUTUZUMAB	**100mg**	IV infusion	See Notes above	In 100ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%
Day 2	Methylprednisolone	80mg	IV	Over 15 min	In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion.
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine	10mg	IV	Slow bolus over 1min	
	Ensure adequate hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10^9/L to reduce the risk of TLS.				
	OBINUTUZUMAB	**900mg**	IV infusion	See notes above	In 250ml Sodium Chloride 0.9% Flush line pre and post infusion with Sodium Chloride 0.9%
Day 8	Methylprednisolone (Only for patients with >Grade 3 IRR with the previous infusion OR lymphocyte count>25x10^9/L prior to next treatment)	80mg	IV	Over 15 min	In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion.
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine (Only for patients with an IRR (Grade 1 or more) with the previous infusion)	10mg	IV	Slow bolus over 1min	
	Ensure adequate hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10^9/L to reduce the risk of TLS.				
	OBINUTUZUMAB	**1000mg**	IV infusion	See notes above	In 250ml Sodium Chloride 0.9% Flush line pre and post infusion with Sodium Chloride 0.9%

Cycle 1 continued

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 15	Methylprednisolone (Only for patients with >Grade 3 IRR with the previous infusion OR lymphocyte count>25x10^9/L prior to next treatment)	80mg	IV	Over 15 min	In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion.
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine (Only for patients with an IRR (Grade 1 or more) with the previous infusion)	10mg	IV	Slow bolus over 1min	
	Ensure adequate hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10^9/L to reduce the risk of TLS.				
	OBINUTUZUMAB	**1000mg**	IV infusion	See notes above	In 250ml Sodium Chloride 0.9% Flush line pre and post infusion with Sodium Chloride 0.9%

TTO cycle 1 only

TTO	Drug	Dose	Route	Directions
Day 1	Allopurinol	300mg	PO	OD, starting 24hrs before first cycle and reviewed after 4 weeks
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose)
	Fluconazole	100mg	PO	OD (plus 3 more months after completion of last obinutuzumab treatment dose)
	CHLORAMBUCIL	**0.5mg/kg/day**	PO	Once daily on Day 1 and 15 as directed. Available as 2mg tablets

Cycle 2-6

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Methylprednisolone (Only for patients with >Grade 3 IRR with the previous infusion OR lymphocyte count>25x10^9/L prior to next treatment)	80mg	IV	Over 15 min	In 100ml Sodium Chloride 0.9%. Infusion **must be completed at least 1 hour prior to the obinutuzumab infusion.**
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine	10mg	IV	Slow bolus over 1min	
	Ensure adequate hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10^9/L to reduce the risk of TLS.				
	OBINUTUZUMAB	**1000mg**	IV infusion	See Notes above	In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%

TTO cycle 2-6

TTO	Drug	Dose	Route	Directions
Day 1	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose)
	Fluconazole	100mg	PO	OD (plus 3 more months after completion of last obinutuzumab treatment dose)
	CHLORAMBUCIL	**0.5mg/kg/day**	PO	Once daily on Day 1 and 15 as directed. Available as 2mg tablets.