Indication	For the treatment of untreated chronic lymphatic leukaemia (CLL) or small lymphocytic lymphoma (SLL) either: • in the presence of 17p deletion and/or *TP53* mutation, • in the absence of 17p deletion and *TP53* mutation suitable or unsuitable for either FCR (fludarabine, cyclophosphamide and rituximab) or BR (bendamustine and rituximab) treatment.
Treatment Intent	Disease Modification.
Frequency and number of cycles	Repeat every 28 days Obinutuzumab: maximum of 6 cycles Venetoclax: 5 weeks titration of venetoclax starting on day 22 of cycle 1 and completing on day 28 of cycle 2. Continue venetoclax until disease progression or unacceptable toxicity or patient choice to stop treatment or for the maximum treatment duration of 12 cycles. Formal medical review as to whether treatment should continue should be scheduled to take place by the end of the first 8 weeks of treatment.
Monitoring Parameters pre-treatment	• Check virology status prior to start of treatment. • **Bloods cycle 1:** ○ Monitor FBC, U&Es and LFTs Day 1, Day 8, Day 15 and Day 22. Tumour Lysis Syndrome assessment should be followed from day 22, blood chemistry monitoring should be performed as per TLS guidance below. • **Bloods cycle 2:** ○ Monitor FBC, U&Es and LFTs weekly. • **Bloods cycle 3 onwards:** ○ Monitor FBC, U&Es and LFTs prior to each cycle or as clinically indicated. • Neuts must be >/= 0.5 and PLT must be >/=25. • U&Es (potassium, uric acid, phosphorous, calcium and creatinine) should be assessed prior to the initial dose to evaluate kidney function and correct pre-existing abnormalities. • **Haematological toxicity:** ○ <u>Obinutuzumab -</u> After first neutropenic event, subsequent cycles should be given prophylactic GCSF. Patients who experience neutropenia should be closely monitored; it is recommended that patients with severe neutropenia lasting more than 1 week receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. 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) may occur. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. ○ <u>Venetoclax</u> – see dose modification section • **<u>Tumour Lysis Syndrome (TLS)</u>** • A tumour burden assessment must take place prior to initiation of venetoclax, to include radiographic evaluation. • Changes in electrolytes consistent with TLS can occur as early as 6 to 8 hours following the first dose and at each dose increase. Patients with a high tumour burden (>25 x 10^9/L) and reduced renal function (CrCl <80ml/min) are at greatest risk of TLS. All patients should have white cell count less than 25 × 10^9/L prior to initiation of venetoclax. Cytoreduction prior to treatment may be required.

- For patients at risk of tumour lysis syndrome (TLS), electrolyte abnormalities should be corrected promptly. The next venetoclax dose should not be administered until the 24 hour blood chemistry results have been evaluated.
- For **low to medium** risk patient's blood chemistries should be monitored pre-dose, and at 6 to 8 hours and at 24 hours for the first dose of 20mg and 50mg, for subsequent dose increases blood chemistries should be taken pre-dose only. For patients who continue to be at risk continue to follow the monitoring schedule for the first dose.
- For **high** risk patients blood chemistries should be monitored pre-dose, and at 4 hours, 8 hours, 12 hours and 24 hours for the first dose of 20mg and 50mg only. For subsequent dose increases blood chemistries should be monitored pre-dose, 6 to 8 hours and at 24 hours.
- Anti-hyperuricaemic agents should be administered prior to starting treatment and be continued for the first 3 cycles and beyond as clinically appropriate. Rasburicase, if required, should be initiated by a consultant. Review and amend as necessary allopurinol prescription.
- All patients should be adequately hydrated during the dose titration phase of venetoclax to reduce the risk of TLS. Patients should be particularly instructed to drink 1.5 - 2 litres of water daily, 2 days prior to and the days of dosing at initiation and each subsequent dose increase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pre-treatment lactate dehydrogenase (LDH) levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose.
- **Hepatic impairment**
  - Obinutuzumab has not been studied in patients with impaired hepatic function, no recommendation available.
  - Venetoclax: No dose adjustment for mild to moderate but close monitoring required in moderate impairment for signs of toxicity at initiation and during titration. A dose reduction of at least 50% is recommended in severe impairment.
- **Renal impairment:**
  - Obinutuzumab: no dose adjustment is required if CrCl >/= 30ml/min; there is no data for CrCl < 30ml/min.
  - Venetoclax: No dose adjustment for mild to moderate (CrCl >/=30ml/min and <90ml/min). Patients with reduced renal function (CrCl <80ml/min) may require extra support and monitoring for TLS during induction and titration phase. Patients with severe renal impairment (CrCl<30ml/min) should only be administered venetoclax if the benefits outweigh the risks and they should be monitored more closely for signs of toxicity and TLS.
- **Obinutuzumab infusion guidance:**
- Patients with a history of cardiac disease should be monitored closely.
- Due to the risk of hypotension during infusion withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each infusion and for the first hour after administration.
- 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.
- **DAY ONE cycle 1: Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.**
  - 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 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. • **Management of adverse reactions and dose adjustments:** ○ Obinutuzumab: no recommend dose adjustments. ○ Venetoclax: If a patient experiences blood chemistry changes suggestive of TLS, the following day's venetoclax dose should be withheld. If resolved within 24 to 48 hours of last dose, treatment with venetoclax can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see Table 1). When resuming treatment after

interruption due to TLS, the instructions for prevention of tumour lysis syndrome should be followed (see above).

Treatment with Venetoclax should be withheld for any grade 3 or 4 non-haematological toxicities, grade 3 or 4 neutropenia with infection or fever, or grade 4 haematological toxicities, except lymphopenia. Once the toxicity has resolved to grade 1 or baseline level (recovery), therapy with venetoclax may be restarted at the same dose. If the toxicity recurs, and for any subsequent occurrences, the dose reduction guidelines in Table 1 should be followed when resuming treatment following resolution. A larger dose reduction may be made at clinician discretion. For patients who require dose reductions to less than 100 mg for more than 2 weeks, discontinuation of venetoclax should be considered.

- For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose titration or more than 2 weeks after completing the dose-titration phase, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g. all or some levels of the dose titration; see Table 1).
- **Progressive multifocal leukoencephalopathy (PML):** PML has been reported in patients receiving obinutuzumab. Patients should be monitored for new or worsening neurological, cognitive or behavioural changes. All treatment should be held if PML is suspected and permanently discontinued if PML is confirmed.

- **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:**
  - **Venetoclax:** Concomitant use with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities. Concomitant use with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole) at initiation and during the dose-titration phase is contraindicated. Concomitant use with moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) at initiation and during the dose-titration phase should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation and titration doses of venetoclax should be reduced by at least 50%. Patients should be monitored more closely for signs of toxicities. For patients who are on a steady daily dose, the venetoclax should be reduced by 50% when used concomitantly with moderate CYP3A inhibitors and by 75% when used concomitantly with strong CYP3A inhibitors.

    Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor.

    Concomitant use of venetoclax with strong (e.g., carbamazepine, phenytoin, rifampin) or moderate (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) CYP3A4 inducers should be avoided. Concomitant use of preparations containing St John's Wort is contraindicated.

    Co-administration of bile acid sequestrants with venetoclax is not recommended.

    It is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin.

    Inhibitors of P-gp or BCRP may increase venetoclax exposure; these should be avoided at initiation of treatment and during the titration phase.

    Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, dabigatran, everolimus, sirolimus) with venetoclax should be avoided.
  - If statins are given concomitantly with venetoclax monitor for statin toxicity.
  - Avoid grapefruit products, Seville oranges and starfruit.
  - **Obinutuzumab:** No formal drug-drug interaction studies have been performed.
- **Missed dose:**

	• If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. • If a patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day. • If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day. • Live vaccines should not be administered during treatment and thereafter until B-cell recovery. • Complete Obinutuzumab monitoring/administration details. • Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment. • The patient should be provided with the Venclyxto® Patient Alert card with each • prescription.
References	KMCC protocol HAEM-CLL-034 v1 KMCC protocol HAEM-NHL-083 SPC accessed online 05.11.2021 Blueteq forms accessed online 05.11.2021

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

Table 1: Dose modification of venetoclax for TLS and other toxicities

Dose at interruption (mg)	**Restart dose (mg[a])**
400	300
300	200
200	100
100	50
50	20
20	10
[a]The modified dose should be continued for 1 week before increasing the dose.	

Cycle 1: 28 day cycle

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 IV 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**	IVI	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 1 min	
	Ensure adequate IV 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	See notes above	In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%
Day 8	Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10^9/L	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 Omit if patient tolerated previous obinutuzumab infusion.	10mg	IV	Slow bolus over 1 min	
	Ensure adequate IV 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**	IVI	See notes above	In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%

Day 15	Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10^9/L	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 Omit if patient tolerated previous obinutuzumab infusion.	10mg	IV	Slow bolus over 1min	
	Ensure adequate IV 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**	IVI	See notes above	In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%
Day 22	**Venetoclax titration**	See TTO	PO		
TTO	Drug	Dose	Route	Directions	
Start titration on day 22 of cycle 1	**VENETOCLAX** (available as 10mg, 50mg and 100mg tablets)	See administration details For escalation schedule.	PO	Start on day 22 of cycle 1 and continue titration through cycle 2. Take 20mg OD for 1 week. Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing. During dose titration the dose should be taken in the morning.	
	Metoclopramide	10mg	PO	Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.	
	Allopurinol	300mg	PO	OD, Start 24 hours before treatment. For the first 3 cycles based on clinical judgement of tumour burden eg WBC count, extent of lymphadenopathy Review if alternative anti-hyperuricaemic agent required. If Rasburicase is needed, then hold Allopurinol. Re-start allopurinol after uric acid levels have settled and Rasburicase has been stopped.	
	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)	
	Consider prophylactic anti-fungal				

Cycle 2: 28 day cycle

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10^9/L	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 Omit if patient tolerated previous obinutuzumab infusion.	10mg	IV	Slow bolus over 1 min	
	Ensure adequate IV 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**	IVI	See notes above	In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%
TTO	Drug	Dose	Route	Directions	
	VENETOCLAX (available as 10mg, 50mg and 100mg tablets)	See administration details For escalation schedule.	PO	**Continue titration dose:** 50mg OD for 1 week then 100mg OD for 1 week then 200mg OD for 1 week then 400mg OD Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing. During dose titration the dose should be taken in the morning.	
	Metoclopramide	10mg	PO	Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.	
	Allopurinol	300mg	PO	OD for the first 3 cycles based on clinical judgement of tumour burden eg WBC count, extent of lymphadenopathy Review if alternative anti-hyperuricaemic agent required.	
	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)	
	Consider prophylactic anti-fungal				

Cycle 3-6 repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10^9/L	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 Omit if patient tolerated previous obinutuzumab infusion.	10mg	IV	Slow bolus over 1 min	
	Ensure adequate IV 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**	IVI	See notes above	In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%
TTO	Drug	Dose	Route	Directions	
Day 1	**VENETOCLAX** (available as 10mg, 50mg and 100mg tablets)	400mg	PO	400mg OD Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing.	
	Metoclopramide	10mg	PO	Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.	
	Allopurinol	300mg	PO	OD for the first 3 cycles based on clinical judgement of tumour burden e.g. WBC count, extent of lymphadenopathy. Review if required.	
	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).	
	Consider prophylactic anti-fungal				

Cycle 7-12: repeat every 28 days

TTO	Drug	Dose		Directions
Day 1	**VENETOCLAX** (available as 10mg, 50mg and 100mg tablets)	400mg	PO	400mg OD Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing.
	Metoclopramide	10mg	PO	Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	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).
	Consider prophylactic anti-fungal			