Indication	Acalabrutinib in combination with venetoclax for the 1st line treatment of previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). NB Patients who have started first line ibrutinib in combination with venetoclax may switch over to acalabrutinib if ibrutinib has been permanently discontinued solely due to severe, dose limiting, or unacceptable toxicity. If there has been disease progression this switch is not permitted.
Treatment Intent	Disease Modification
Frequency and number of cycles	28 day cycle Cycle 1 and 2 acalabrutinib monotherapy Cycle 3 to 14 acalabrutinib in combination with venetoclax Continue until disease progression, unacceptable toxicity, patient choice to stop, or reaching the maximum specified fixed duration (14 cycles of acalabrutinib / 12 cycles of venetoclax) whichever occurs sooner.
Monitoring Parameters	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • **FBC** on day 1 of cycle 1 and cycle 2. For cycle 3 and cycle 4, monitor **FBC** every day or on alternate days for the first week (of cycle 3) and then weekly. From cycle 5 onwards, check **FBC** at the beginning of each cycle or as clinically indicated. Neuts must be >/= 0.5 and PLT must be >/=25. Monitoring may be extended to 3 monthly for stable patients. • **U&Es** and **LFTs** at each cycle. U&Es (potassium, uric acid, phosphorous, calcium and creatinine) should be assessed prior to the initial dose of venetoclax to evaluate kidney function and correct pre-existing abnormalities. Blood chemistries should be reassessed prior to each subsequent dose increase during the titration phase. • **ECG** baseline in patients with cardiac history. • **Hepatic impairment:** o **Acalabrutinib:** Avoid administration of acalabrutinib in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3xULN and any AST). Dose modifications are not required for patients with mild or moderate hepatic impairment (Child-Pugh A, Child-Pugh B, or total bilirubin between 1.5-3x ULN and any AST), however patients with moderate impairment should be monitored closely for signs of toxicity. o **Venetoclax:** No dose adjustment for mild to moderate but close monitoring required for moderate impairment for signs of toxicity at initiation and during titration. A dose reduction of 50% is recommended in severe impairment, with close monitoring for signs of toxicity. • **Renal impairment:** o **Acalabrutinib**: No dose adjustment in mild to moderate renal impairment (CrCl>/=30ml/min). No data in patients with severe renal impairment (CrCl<30ml/min). Treatment should only be administered in patients with severe renal impairment only if the benefit outweighs the risk and these patients should be monitored closely for signs of toxicity. o **Venetoclax:** No dose adjustment for mild to moderate (CrCl >/=30ml/min and <90ml/min). 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 at initiation and titration phase. • **Management of adverse reactions and dose adjustments:** • **Acalabrutinib:** o For Grade 3 or greater non- haematological toxicities, Grade 3 thrombocytopenia (PLT 25-49) with

bleeding, Grade 4 thrombocytopenia (<25) or Grade 4 neutropenia (<0.5) lasting longer than 7 days (supporting neutrophil growth factors could be considered) the recommended dose adjustments are:

- First and Second occurrence - Interrupt acalabrutinib. Once toxicity has resolved to Grade 1 (neuts >/=1, platelets >/= 75) or baseline level, acalabrutinib may be resumed at 100 mg approximately every 12 hours.
- Third occurrence - Interrupt acalabrutinib. Once toxicity has resolved to Grade 1 (neuts >/=1, platelets >/= 75) or baseline level, acalabrutinib may be resumed at a reduced frequency of 100 mg once daily.
- Fourth occurrence - Discontinue acalabrutinib.
- **Haemorrhage:** Use with caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Consider withholding acalabrutinib for 3 days pre and post-surgery depending on the type of surgery and the risk of bleeding.
- **Progressive multifocal leukoencephalopathy (PML):** PML has been reported in patients receiving acalabrutinib. 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.
- **Sun exposure:** Monitor patients for skin cancers and advise protection.
- Monitor for symptoms of **arrhythmia** (e.g. palpitations, dizziness, syncope, dyspnoea) and manage as appropriate. The risk of arrhythmia may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection.

- **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 below).
  - 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 when at the daily dose of 400 mg, 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).
- **Tumour Lysis Syndrome (TLS)**
  - A tumour burden assessment must take place prior to initiation of venetoclax. Consider re-imaging to assess TLS risk in selected patients e.g. those with bulky disease, prior to commencing venetoclax in cycle 3.
  - Tumour Lysis Syndrome is a particular risk in the initial 5-week dose titration phase. 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 (any lymph node with a diameter >/=5cm or lymphocyte count >/=25 x 10^9/L) are at greater risk of TLS. Reduced renal function (CrCl <80ml/min) further increases the risk. Based on the risk of TLS, patients may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring.
  - 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 patients, 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 2 to 3 days prior to starting treatment with venetoclax in patients with high uric acid levels or at risk of TLS and may be continued through the titration phase. Rasburicase, if required, should be initiated by a consultant. Review and amend as necessary allopurinol prescription.
- Patients should be adequately hydrated during the dose titration phase 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.

- **Common drug interactions (for comprehensive list refer to BNF/SPC):**
- **Acalabrutinib:**
  - Avoid concomitant use of strong CYP3A inhibitors (e.g. ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole), if the short-term use of a strong CYP3A inhibitor cannot be avoided, interrupt treatment with acalabrutinib. If a moderate CYP3A inhibitor is required monitor closely for adverse reactions.
  - Avoid concomitant use with strong CYP3A inducers (e.g. phenytoin, rifampicin, and carbamazepine).
  - Avoid grapefruit, grapefruit juice and Seville oranges.
  - Concomitant use of preparations containing St John's Wort should be avoided.
  - Warfarin or other vitamin K antagonists should not be administered concomitantly.
- **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, rifampicin) 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 and should be avoided at initiation and during titration.
  - Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, dabigatran,

	everolimus, sirolimus) with venetoclax should be avoided. ○ Avoid grapefruit products, Seville oranges and starfruit. ○ Live vaccines should not be administered during treatment and thereafter until B-cell recovery. • **Missed dose:** • **Acalabrutinib:** ○ If the dose has been missed by less than 3 hours the patient should take their usual dose. If more than 3 hours have passed, the patient should be instructed to miss that dose and take next dose of acalabrutinib at the usual time. Do not take extra to make up for the missed dose. • **Venetoclax:** ○ 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 of venetoclax, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day. • **Pregnancy and contraception:** • Women of childbearing potential should be advised to avoid becoming pregnant while receiving venetoclax and acalabrutinib and for at least 30 days after the last dose of venetoclax. Women using hormonal contraceptives should add a barrier method, it is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives. • **Driving and machinery:** Venetoclax and acalabrutinib can both cause dizziness and fatigue patients who experience these symptoms should be advised not to drive or operate machinery until symptoms subsided. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet. • **Patient information documents.** The patient should be provided with the Venclyxto® Patient Alert card with each prescription.
References	KMCC protocol HAEM-CLL-039 V1 Ref for V1 SPC accessed online 12.08.2026 Calquence 100 mg film-coated tablets CDF list V1.406 accessed online 12.08.2026 SPC accessed online 17.08.2026 Venclyxto 100mg tablets

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

Table 1 SPC recommended dose modification for 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 and 2 only: repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**ACALABRUTINIB**	**100mg**	PO	BD Should be swallowed whole with a glass of water. Do not crush, chew, dissolve or split the tablets. Available as 100mg tablets.
	Allopurinol	300mg	PO	OD.
	Metoclopramide	10mg	PO	Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2mg-4mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 then only if required.
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays.
	Aciclovir	400mg	PO	BD
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors.			

Cycle 3: Week 1

The starting dose is 20 mg of venetoclax once daily for 7 days. The dose must be gradually increased over a period of 5 weeks up to the recommended daily dose of 400 mg.

TTO	Drug	Dose	Route	Directions
Day 1	**ACALABRUTINIB**	**100mg**	PO	BD Should be swallowed whole with a glass of water. Do not crush, chew, dissolve or split the tablets. Available as 100mg tablets.
	VENETOCLAX	**20mg**	PO	OM for 7 days 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. Available as 10mg, 50mg and 100mg tablets.
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Allopurinol	300mg	PO	OD for the first 2 – 3 cycles of venetoclax based on clinical judgement of tumour burden e.g. 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.
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays.
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Cycle 3: Week 2

TTO	Drug	Dose	Route	Directions
Day 8	**ACALABRUTINIB**	**100mg**	PO	BD Should be swallowed whole with a glass of water. Do not crush, chew, dissolve or split the tablets. Available as 100mg tablets.
	VENETOCLAX	**50mg**	PO	OM for 7 days 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. Available as 10mg, 50mg and 100mg tablets.
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Allopurinol	300mg	PO	OD for the first 2 – 3 cycles of venetoclax based on clinical judgement of tumour burden e.g. WBC count, extent of lymphadenopathy. Review if alternative anti-hyperuricaemic agent required.
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays.
	Loperamide	2mg-4mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 then only if required.
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Cycle 3: Week 3

TTO	Drug	Dose	Route	Directions
Day 15	**ACALABRUTINIB**	**100mg**	PO	BD Should be swallowed whole with a glass of water. Do not crush, chew, dissolve or split the tablets. Available as 100mg tablets.
	VENETOCLAX	**100mg**	PO	OM for 7 days 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. Available as 10mg, 50mg and 100mg tablets.
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Allopurinol	300mg	PO	OD for the first 2 – 3 cycles of venetoclax based on clinical judgement of tumour burden e.g. WBC count, extent of lymphadenopathy. Review if alternative anti-hyperuricaemic agent required.
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays.
	Loperamide	2mg-4mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 then only if required.
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Cycle 3: Week 4

TTO	Drug	Dose	Route	Directions
Day 22	**ACALABRUTINIB**	**100mg**	PO	BD Should be swallowed whole with a glass of water. Do not crush, chew, dissolve or split the tablets. Available as 100mg tablets.
	VENETOCLAX	**200mg**	PO	OM for 7 days. 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. Available as 10mg, 50mg and 100mg tablets.
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Allopurinol	300mg	PO	OD for the first 2 – 3 cycles of venetoclax based on clinical judgement of tumour burden e.g. WBC count, extent of lymphadenopathy. Review if alternative anti-hyperuricaemic agent required.
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays.
	Loperamide	2mg-4mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 then only if required.
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Cycle 4 to 14
Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**ACALABRUTINIB**	**100mg**	PO	BD Should be swallowed whole with a glass of water. Do not crush, chew, dissolve or split the tablets. Available as 100mg tablets.
	VENETOCLAX	**400mg**	PO	OM for 28 days 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. Available as 10mg, 50mg and 100mg tablets.
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Allopurinol	300mg	PO	OD for the first 2 – 3 cycles of venetoclax based on clinical judgement of tumour burden e.g. WBC count, extent of lymphadenopathy. Review if alternative anti-hyperuricaemic agent required.
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays.
	Loperamide	2mg-4mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 then only if required.
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			