Indication	Chronic lymphatic leukaemia or small lymphocytic lymphoma requiring treatment in the **PRESENCE** of 17p deletion or TP53 mutation or **ABSENCE** of 17p deletion (and absence of TP53 mutation if tested) following progressive disease on or after chemoimmunotherapy and/or a B cell receptor pathway inhibitor: a Bruton's tyrosine kinase inhibitor (BTKi eg ibrutinib) or a PI3K inhibitor (PI3Ki e.g. idelalisib) or have a contraindication to receiving both a BTKi and a PI3Ki. NB: if previously treated with venetoclax in combination with obinutuzumab or venetoclax in combination with rituximab or venetoclax in combination with ibrutinib, the patient must not have progressed during these treatments.
Treatment Intent	Disease Modification
Frequency and number of cycles	Every 28 days. Continue until progressive disease or unacceptable toxicity, whichever occurs first.
Monitoring parameters pre-treatment	• Monitor FBC every day or on alternate days for the first week, then every week for the first 6 weeks, and then at the beginning of 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. Blood chemistries should be reassessed prior to each subsequent dose increase during the titration phase • **Tumour Lysis Syndrome (TLS)** • A tumour burden assessment must take place prior to initiation of venetoclax, to include radiographic evaluation. • 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 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 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. • **Renal impairment:** 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. • **Hepatic impairment:** 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. • **Dose modifications and toxicities:** • 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 occurences, 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). • **Common drug interactions (for comprehensive list refer to BNF/SPC):** 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 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. • **Missed doses**: • 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. • 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.
Reference(s)	KMCC protocol HAEM-CLL-030 V2 SPC accessed online 24.03.2023

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

Table 1: Dose modification 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.	

Repeated every 28 days

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.

CYCLE 1: Week 1

TTO	Drug	Dose	Route	Directions
Day 1	**VENETOCLAX** (available as 10mg, 50mg and 100mg tablets)	**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.
	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	Start 2 to 3 days before treatment with venetoclax. od for the first 2 – 3 cycles 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.

Week 2

TTO	Drug	Dose	Route	Directions
Day 8	**VENETOCLAX** (available as 10mg, 50mg and 100mg tablets)	**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.
	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 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

Week 3

TTO	Drug	Dose	Route	Directions
Day 15	**VENETOCLAX** (available as 10mg, 50mg and 100mg tablets)	**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.
	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 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

Week 4

TTO	Drug	Dose	Route	Directions
Day 22	**VENETOCLAX** (available as 10mg, 50mg and 100mg tablets)	**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.
	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 based on clinical judgement of tumour burden eg WBC count, extent of lymphadenopathy Review if alternative anti-hyperuricaemic agent required
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays

Cycle 2 onwards: repeat every 28 days

Week 5 and beyond

TTO	Drug	Dose	Route	Directions
Day 1	**VENETOCLAX** (available as 10mg, 50mg and 100mg tablets)	**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.
	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 based on clinical judgement of tumour burden eg WBC count, extent of lymphadenopathy Review if alternative anti-hyperuricaemic agent required
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays

Protocol No	HAEM-CLL-030	Kent and Medway SACT Protocol Disclaimer: No responsibility will be accepted for the accuracy of this information when used elsewhere.	
Version	V3	Written by	M.Archer
Supersedes version	V2	Checked by	H.Paddock (V3) O.Okuwa (V1) V2 and V3 up dated in line with SPC update and commissioning criteria
Date	26.05.2023	Authorising consultant (usually NOG Chair)	J.Osborne (V1) L.Banerjee (V1)