Indication	First line treatment of previously untreated CLL
Treatment Intent	Disease modification
Frequency and number of cycles	28 day cycle Cycle 1-3 Ibrutinib monotherapy. Cycle 4-15 Venetoclax* and Ibrutinib combination therapy. * 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. Continue until disease progression or unacceptable toxicity or patient choice to stop treatment, for a maximum of 15 cycles of ibrutinib and 12 cycles of venetoclax.

Monitoring Parameters pre-treatment	• **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.
	• **ECG baseline.** Further cardiac evaluation including an ECHO should be considered in patients with cardiac risk factors or previous anthracycline therapy.
	• BP to be monitored every cycle.
	• **Cycle 1-3:** FBC, LFTs, creatinine, urea and electrolytes should be measured before each cycle. Proceed with next cycle if ANC >/= 0.5 x 10^9/L and platelets >/= 25 x 10^9/L. If counts below these check with consultant.
	• **Cycle 4 onwards:** 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. Proceed with next cycle if ANC >/= 0.5 x 10^9/L and platelets >/= 25 x 10^9/L. If counts below these check with consultant.
	• 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. Refer to TLS monitoring section below as blood chemistries taken dependent upon risk category of patient.
	• **Renal impairment:**
	  ○ **Ibrutinib -** No dose adjustment for patients with CrCl>30ml/min. No data in patients with CrCl<30ml/min, use only if benefit outweighs risk. Monitor closely for signs of toxicity.
	  ○ **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**.**
	• **Hepatic Impairment:**
	  ○ **Ibrutinib –** Ibrutinib is metabolised in the liver. For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily. For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily. Monitor patients for signs of toxicity and follow dose modification guidance as needed (see SPC). It is not recommended to administer Ibrutinib to patients with severe hepatic impairment (Child-Pugh class C).
	  ○ **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.

- **Dose adjustments:**
  - **Ibrutinib:** Should be withheld if neutrophils < 1.0 x 10^9/l with infection or fever, or any grade 4 haematological toxicity (e.g. neutrophils < 0.5 x10^9/l or platelets < 25 x 10^9/l). Withhold ibrutinib for any new onset or worsening grade >/=3 non-haematological toxicity. Once toxicity has resolved to Grade 1 or baseline, ibrutinib may be re-started, following table 2 below. If the toxicity reoccurs, the once daily dose should be reduced by 140 mg. A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue the medicinal product.
  - **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).
- **Management of adverse reactions**
- **Ibrutinib**
  - **Cardiac arrhythmia and cardiac failure:**
    Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia and cardiac failure have been reported in patients treated with ibrutinib. Periodically monitor all patients clinically for cardiac manifestations including arrhythmia and cardiac failure. In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, ibrutinib should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.
  - **Bleeding:** Monitor patient closely for any signs and symptoms of bleeding. Treatment should be held 3 to 7 days pre and post-surgery dependant on type of surgery.
  - **Interstitial Lung Disease (ILD):**
    Cases of ILD have been reported in some patients. Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt treatment and manage ILD appropriately. If symptoms persist, consider the risks and benefits of treatment and follow the dose modification guidelines (see SPC).
    Cases of invasive fungal infections, including cases of Aspergillosis, Cryptococcosis and Pneumocystis jiroveci infections have been reported following the use of ibrutinib.
  - **Splenic rupture:**
    Cases of splenic rupture have been reported following discontinuation of ibrutinib. Disease status and spleen size should be carefully monitored (e.g. clinical examination, ultrasound) when treatment is interrupted/discontinued. Patients who develop left upper abdominal or shoulder tip pain should be assessed and splenic rupture should be considered.

- **Venetoclax**
  - 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 and lymphocyte count >/=25 x 10^9/L or any lymph node with a diameter >/=10cm) 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.
- **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:**
- **Ibrutinib:**
  - Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib.
  - Patient receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising. Ibrutinib should be withheld in the event of any bleeding events.
  - Ibrutinib is metabolised by CYP3A4. Avoid concomitant use of strong (ketoconazole, clarithromycin, itraconazole and ritonavir) or moderate (fluconazole, erythromycin, amprenavir, aprepitant and atazanavir) CYP3A4 inhibitors. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the dose to 140mg for the duration of the inhibitor use or withhold ibrutinib temporarily (for 7 days or less). If a moderate CYP3A4 inhibitor is indicated, reduce ibrutinib dose to 280mg for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid moderate or strong inducers (e.g. carbamazepine, rifampicin, phenytoin, and St. John's Wort).
  - To minimise the potential for an interaction in the GI tract, oral narrow therapeutic range, P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib.
  - Do not take with grapefruit juice or Seville oranges.
  - Supplements such as fish oil and vitamin E preparations should be avoided.

	• **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 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:**
	• **Ibrutinib** - If a dose is missed it should be taken as soon as possible on the same day and the patient should return to the normal schedule the following day.
	• **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.
	• **Driving:** Patients should be advised to be cautious when driving or using machines treatment with ibrutinib and venetoclax may affect their ability.
	• **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	CDF list V1.260 accessed online 22.04.2023 KMCC protocol HAEM-CLL-029 V6 KMCC protocol HAEM-CLL-030 V2 SPC accessed online 22.04.2023 https://clinicaltrials.gov/ct2/show/NCT03462719

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

Table 1: Venetoclax 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.	

Table 2: Ibrutinib recommended dose modifications

Toxicity Occurrence	CLL dose modification after recovery
First	Restart at 420mg daily
Second	Restart at 280mg daily
Third	Restart at 140mg daily
Fourth	Discontinue ibrutinib

Cycle 1-3 only
Repeat every 28 days

Day	Drug	Dose	Route	Administration
1	**IBRUTINIB**	**420mg**	PO	To be taken once a day at approximately the same time each day. Swallow whole with water. Available as **420mg, 280mg and 140mg** tablets.
	Allopurinol	300mg	PO	OD for 4 weeks. Dispense on **cycle 1**, omit cycle 2 and 3 and then restart at **cycle 4.**
	Metoclopramide	10mg	PO	TDS PRN Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Co-trimoxazole	480mg	PO	BD on a Monday Wednesday and Friday only.
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Cycle 4: 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	**IBRUTINIB**	**420mg**	PO	To be taken once a day at approximately the same time each day. Swallow whole with water. Available as **420mg, 280mg and 140mg** tablets.
	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 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 4: Week 2

TTO	Drug	Dose	Route	Directions
Day 8	**IBRUTINIB**	**420mg**	PO	To be taken once a day at approximately the same time each day. Swallow whole with water. Available as **420mg, 280mg and 140mg** tablets.
	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 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
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Cycle 4: Week 3

TTO	Drug	Dose	Route	Directions
Day 15	**IBRUTINIB**	**420mg**	PO	To be taken once a day at approximately the same time each day. Swallow whole with water. Available as **420mg, 280mg and 140mg** tablets.
	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 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
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Cycle 4: Week 4

TTO	Drug	Dose	Route	Directions
Day 22	**IBRUTINIB**	**420mg**	PO	To be taken once a day at approximately the same time each day. Swallow whole with water. Available as **420mg, 280mg and 140mg** tablets.
	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 of venetoclax 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
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Cycle 5 to 15
Repeat every 28 days

TTO	Drug	Dose	Route	Directions
	IBRUTINIB	**420mg**	PO	To be taken once a day at approximately the same time each day. Swallow whole with water. Available as **420mg, 280mg and 140mg** tablets.
	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 of venetoclax 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
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			