Indication	For previously treated CLL or SLL either: • in the presence of 17p deletion or *TP53* mutation in adult patients who have failed a B-cell receptor pathway inhibitor, or • in the absence of 17p deletion or *TP53* mutation in adult patients who have failed anti-CD20-containing chemoimmunotherapy (Nb The patient should not have received venetoclax whether as monotherapy or in combination with rituximab or any other anti-CD20 monoclonal antibody).
Treatment Intent	Disease modification
Frequency and number of cycles	Cycle 1: 5 weeks titration of venetoclax then every 28 days from cycle 2 Continue until progressive disease or unacceptable toxicity or for the maximum treatment duration of 2 years of venetoclax (as measured from the 1st day of administration of rituximab) whichever occurs first. Maximum 6 cycles of rituximab.
Monitoring Parameters pre-treatment	• Check virology status prior to start of 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 and prior to each cycle as clinically indicated. • For patients at risk of tumour lysis syndrome (TLS), blood chemistries should be monitored at 6 to 8 hours and at 24 hours after the first dose. Electrolyte abnormalities should be corrected promptly. The next venetoclax dose should not be administered until the 24 hour blood chemistry results have been evaluated. The same monitoring schedule should be followed at the start of the 50mg dose and then for patients who continue to be at risk at subsequent dose increases. • Patients with a high tumour burden or with a high number of lymphocytes (>25 x 10^9/l) who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split rituximab dosing over two days during the first cycle. • **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. • 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 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.
- **Hepatic impairment**: No dose adjustment for mild to moderate but close monitoring required in moderate impairment for signs of toxicity at initiation and during titration. Not recommended in severe hepatic impairment
- **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.

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.

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).

- **Drug interactions:** 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. • **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. • A 6 week break is only permitted to allow any treatment toxicity to settle or comorbidities to improve. Treatment breaks of more than 6 weeks beyond the expected cycle length are not allowed. • Live vaccines should not be administered during treatment and thereafter until B-cell recovery. • Ensure pre-medication of Rituximab with Chlorphenamine, hydrocortisone & paracetamol. Monitor Rituximab infusion closely (complete monitoring form), watch for signs of dyspnoea, fever, rigors. If such symptoms occur stop infusion and seek medical advice. Infusion may be recommenced at half the previous rate, once symptoms have subsided. Anaphylaxis drugs must be available when treating with Rituximab. • Consider withdrawing any anti-hypertensives 12 hours before treatment with Rituximab.
References	KMCC protocol HAEM-CLL-030 CDF list v1.121 KMCC proforma HAEM-NHL-026 v1 SPC accessed online 21/01/2019

NB For funding information, refer to the SACT funding spread sheet

Cycle 1 - Titration of venetoclax

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.

Week 1

TTO	Drug	Dose	Route	Administration
	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 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.
	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	Administration
	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	Take 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

Week 3

TTO	Drug	Dose	Route	Administration
	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	Take 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

Week 4

TTO	Drug	Dose	Route	Administration
	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	Take 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

Week 5

TTO	Drug	Dose	Route	Administration
	Venetoclax (available as 10mg, 50mg and 100mg tablets	**400mg**	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	Take 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 (cycle length 28 days)

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Paracetamol	1000mg	PO	STAT	
	Chlorphenamine	10mg	IV	1 min	By slow IV infusion
	Hydrocortisone	100mg	IV	STAT	
	Commence rituximab at least 30 mins – 1 hour after pre-medication				
	Rituximab	**375mg/m²**	IV	Initiate at 50mg/hr. Increase at 50mg/hr increments every 30mins to 400mg/hr max	Sodium Chloride 0.9% 500ml

TTO	Drug	Dose	Route	Directions
	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.
	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
	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 3-7 (repeated every 28 days)

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Paracetamol	1000mg	PO	STAT	
	Chlorphenamine	10mg	IV	1 min	By slow IV infusion
	Hydrocortisone	100mg	IV	STAT	
	Commence rituximab at least 30 mins – 1 hour after pre-medication				
	Rituximab	**500mg/m²**	IV	If previously tolerated initiate infusion at 100mg/hr. Increase rate at 100mg/hr increments every 30mins to 400mg/hr max.	Sodium Chloride 0.9% 500ml
TTO	Drug	Dose	Route	Directions	
	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.	
	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	
	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 8 onwards (repeated every 28 days)

TTO	Drug	Dose	Route	Directions
	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.
	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
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays