Regimen: Venetoclax Monotherapy

Document History		
Version Number	Issue Date	Review date
2.0	05/03/2021	05/03/2024
Changes from previous version: Updated prescriptions and monitoring		
Authors		
Haematologist	Pharmacist	Nurse Specialist

Patient Name	DOB	Hospital No.	Consultant	Allergies

Indications	CLL in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor. CLL in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.
Pre-treatment evaluation checklist	**Mandatory Fields: (Incomplete fields can result in delayed treatment)**

Height (cm)	
Weight (kg)	
Surface Area Dubois (m^2); if adjusted state SA used to dose	
WHO Performance	
Testing for Hepatitis B, Hepatitis C and HIV	Date_____
Sperm banking or oocyte/embryo preservation must be offered to males <55yrs and pre-menopausal women concerned about fertility	☐
Arrangements made to discuss at MDT	Date_____
Baseline imaging requested	☐
ECHO or ECG required	☐
Provide contact details for Clinical Nurse Specialist for further information	☐
Complete Current Medication List and discontinue any inappropriate medication (e.g. immunosuppressive drugs)	☐
Dose modifications considered and/or a Growth-Colony Stimulating Factor. Details:	☐
Cancer care suite informed for date	Date_____
Consented by:	Date_____
Patient given blood form for at least 1 week prior to chemotherapy	☐
CDF form completed if necessary	☐

Consultant / Speciality Doctor Signature _____ Date _____

Investigations prior to each course	FBC, U&Es, LFTs and Bone Profile Specific bloods are required at start of treatment when dose escalating to monitor for Tumour Lysis Syndrome. See full protocol for details

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Current Medication List

Concomitant use of Venetoclax with

- strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated
- bile acid sequestrants with venetoclax is not recommended.
- P-gp, or BCRP substrates (e.g., digoxin, dabigatran, everolimus, sirolimus) with Venetoclax should be avoided.

If any of the above medications then inform Haematology Consultant seek and consult SPC and pharmacy advise

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Drug Regimen				
Week	**Drug**	**Dose**	**Route**	**Comments**
1	Venetoclax	20mg	PO	See below for blood test monitoring around dose increases
2		50mg		
3		100mg		
4		200mg		
5+		400mg		
Cycle Frequency	Once established on treatment dose cycles are 28 days.			

Medication Concurrent	Allopurinol 300mg OD for 3 days prior to starting Venetoclax and continuing until dose escalation has completed and no evidence of biochemical tumour lysis syndrome. Rasburicase may be given for high risk patients instead. Co-Trimoxazole 960mg OD Mon/Wed/Friday for 28 days (480mg if CrCl 15-30mls/min)

Concurrent Medication Prescription									
Date									
	Cycle Day			**Cycle Day**			**Cycle Day**		
Adjuvants	**Dose**	**Dispensed**	**Given by**	**Dose**	**Dispensed**	**Given by**	**Dose**	**Dispensed**	**Given by**
Allopurinol 300mg OD (100mg od if CrCl<20ml/min)									
Co-Trimoxazole 960mg OD Mon/Wed/Friday for 28 days (480mg if CrCl 15-30mls/min)									
Prescribed by:									
Regimen and calculation checked (pharmacist)									
Pharmacist Dispensing date and check									

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Toxicity

System organ class	Frequency (all grades)[a]	Adverse reactions	Grade ≥3[a]
Infections and infestations	Very common	Pneumonia Upper respiratory tract infection	
	Common	Sepsis Urinary tract infection	Sepsis Pneumonia Urinary tract infection Upper respiratory tract infection
Blood and lymphatic system disorders	Very common	Neutropenia Anaemia Lymphopenia	Neutropenia Anaemia
	Common	Febrile neutropenia	Febrile neutropenia Lymphopenia
Metabolism and nutrition disorders	Very common	Hyperkalaemia Hyperphosphataemia Hypocalcaemia	
	Common	Tumour lysis syndrome Hyperuricaemia	Tumour lysis syndrome Hyperkalaemia Hyperphosphataemia Hypocalcaemia Hyperuricaemia
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Nausea Constipation	
	Common		Diarrhoea Vomiting Nausea
	Uncommon		Constipation
General disorders and administration site conditions	Very common	Fatigue	
	Common		Fatigue
Investigations	Common	Blood creatinine increased	
	Uncommon		Blood creatinine increased

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Dose Modifications	
	Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase.

Table 1. Laboratory Tumour Lysis Syndrome

Lab Test	**Change**
Urate	>475 µmol/l or 25% increase from baseline
Potassium	>5.9 mmol/l or 25% increase from baseline
Phosphate	>2.0 mmol/l or 25% increase from baseline
Calcium	<1.76 mmol/l or 25% decrease from baseline

Prevention of tumour lysis syndrome (TLS)

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (e.g., any lymph node with a diameter ≥5 cm or high absolute lymphocyte count [ALC ≥25 x 10^9/l]) are at greater risk of TLS when initiating venetoclax. Reduced renal function (creatinine clearance [CrCl] <80 ml/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment.

Prior to initiating venetoclax, tumour burden assessment, including radiographic evaluation (e.g., CT scan), must be performed for all patients. Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed and pre-existing abnormalities corrected. The prophylaxis measures listed below should be followed. More intensive measures should be employed as overall risk increases.

<u>Hydration</u>

Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink plenty of water daily starting 2 days before and throughout the dose-titration phase. Patients should be particularly instructed to drink 1.5 to 2.0 L 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.

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Anti-hyperuricaemic agents

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.

Laboratory assessments

Pre-dose: For all patients, blood chemistries 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.

Post-dose: For patients at risk of TLS, blood chemistries should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax. 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 50 mg dose and then for patients who continue to be at risk, at subsequent dose increases.

Hospitalisation

Based on physician assessment, some patients, especially those at greater risk of TLS, may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours (see section 4.8). Hospitalisation should be considered for subsequent dose increases based on reassessment of risk.

Dose modifications for tumour lysis syndrome

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 2). When resuming treatment after interruption due to TLS, the instructions for prevention of TLS should be followed (see “Prevention of tumour lysis syndrome” above).

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Dose modifications for other toxicities

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 2 should be followed when resuming treatment with venetoclax following resolution. A larger dose reduction may occur at the discretion of the physician. For patients who require dose reductions to less than 100 mg for more than 2 weeks, discontinuation of venetoclax should be considered.

Table 2.

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 2).

Dose modifications for use with CYP3A inhibitors

Concomitant use of venetoclax 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.

Table 3 describes Venetoclax contraindication or dosage modification based on concomitant use with a strong or moderate CYP3A inhibitor. 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.

Table 3: Management of potential Venetoclax interactions with CYP3A inhibitors

Inhibitors	Initiation and titration phase[a]	Steady daily dose (After titration phase)
CYP3A inhibitor	Contraindicated	Reduce the Venetoclax dose by at least 75%
Moderate CYP3A inhibitor	Reduce the Venetoclax dose by at least 50%	

[a]Avoid concomitant use of Venetoclax with moderate CYP3A inhibitors at initiation and during the dose titration phase. Consider alternative medications or reduce the Venetoclax dose as described in this table.

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TLS Monitoring at start of treatment	**To ensure bloods are monitored pre venetoclax, plus 6 and 24 hours following dose increment.** **Week 1 day 1:** • Patient attends Cancer Care 8am and receives first dose of venetoclax. • Patient remains on the unit for 6 hours at which point repeat bloods are done (U&Es, Bone Profile & Urate). • Liaise with consultant immediately upon receipt of blood results • Depending on blood results, consultant to decide on admission or discharge from cancer care **Week 1 Day 2:** • If not admitted previous day, patient attends Cancer Care 8am for bloods (as above). • Patient waits until results received. • Liaise with consultant immediately upon receipt of blood results • Depending on blood results, consultant to decide on admission or discharge from cancer care • If discharge, Patient given next 6 days supply of venetoclax to take home **Week 2 day 0:** • Patient has bloods checked in community 1-3 days prior to the start of the next dose increase **Week 2 day 1:** • Patient attends Cancer Care 8am and receives first dose of venetoclax. • Patient remains on the unit for 6 hours at which point repeat bloods are done (U&Es, Bone Profile & Urate). • Liaise with consultant immediately upon receipt of blood results • Depending on blood results, consultant to decide on admission or discharge from cancer care **Week 2 Day 2:** • If not admitted previous day, patient attends Cancer Care 8am for bloods (as above). • Patient waits until results received. • Liaise with consultant immediately upon receipt of blood results • Depending on blood results, consultant to decide on admission or discharge from cancer care • If discharge, Patient given next 6 days supply of venetoclax to take home **Week 3 onwards:** • Visits to cancer care for pre and post venetoclax bloods no longer necessary if patient has had no evidence of tumour lysis on previous dose escalations. Otherwise continue with monitoring on day 1 and 2 of each increment.

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Notes	**Women of childbearing potential/Contraception in females** Women should avoid becoming pregnant while taking Venetoclax and for at least 30 days after ending treatment. Therefore, women of childbearing potential must use highly effective contraceptive measures while taking venetoclax and for 30 days after stopping treatment. It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method. **Pregnancy** Based on embryo-foetal toxicity studies in animals, venetoclax may harm the foetus when administered to pregnant women. There are no adequate and well-controlled data from the use of venetoclax in pregnant women. Studies in animals have shown reproductive toxicity. Venetoclax is not recommended during pregnancy and in women of childbearing potential not using highly effective contraception. **Breast-feeding** It is unknown whether venetoclax or its metabolites are excreted in human milk. A risk to the breast-feeding child cannot be excluded. Breast-feeding should be discontinued during treatment with venetoclax. **Fertility** No human data on the effect of venetoclax on fertility are available. Based on testicular toxicity in dogs at clinically relevant exposures, male fertility may be compromised by treatment with venetoclax. Before starting treatment, counselling on sperm storage may be considered in some male patients.
Reference	1) Venetoclax SPC 21/04/2020 https://www.medicines.org.uk/emc/product/2267/smpc

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Case Note Copy

Consent Form 3
Patient agreement to investigation or treatment
(procedure where consciousness not impaired)

Name of Procedure
(Include brief explanation if medical term not clear)

Venetoclax monotherapy

Statement of health professional (to be filled in by health professional with appropriate knowledge of proposed procedure, as specified in consent policy)

I have explained the procedure to the patient. In particular, I have explained:

The intended benefits: Treatment of CLL/SLL, life extension and improved quality of life.

Serious of frequently occurring risks: Infections, Low blood counts, Tumour lysis syndrome, altered bowel habit, nausea and fatigue

I have also discussed what the procedure is likely to involve, the benefits and risks of any available alternative treatments (including no treatment) and any particular concerns of those involved.

☐ **The following leaflet has been provided:** Venetoclax patient information leaflet

Signed:_____ Date:_____

Name (PRINT):_____ Job Title:_____

Statement of interpreter (where appropriate)

I have interpreted the information above to the patient to the best of my ability and in a way in which I believe s/he can understand

Signed:_____ Date:_____ Name (PRINT)_____

Statement of patient

I agree to the procedure described above.
I understand that you cannot give me a guarantee that a particular person will perform the procedure. The person will, however, have appropriate experience.
I understand that the procedure will not involve local anaesthesia.

Signed:_____ Date:_____ Name (PRINT)_____

Confirmation of consent (to be completed by a health professional when the patient is admitted for the procedure, if the patient has signed the form in advance)

I have confirmed that the patient has no further questions and wishes the procedure to go ahead.

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