Venetoclax Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Treatment of chronic lymphocytic leukaemia (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.	C91	00400a	CDS 01/12/2018
Treatment of 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	C91	00400b	CDS 01/12/2018

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Venetoclax is administered orally once a day with a starting dose of 20mg; this is increased every seven days over a period of 5 weeks until a dose of 400mg is reached. Treatment should be continued until disease progression or no longer tolerated by the patient.

The 5-week dose-titration schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of tumour lysis syndrome (TLS)

WEEK	Venetoclax Dose (mg)	Route	Cycle
1	20	PO*	Continuously for 7 days
2	50	PO*	Continuously for 7 days
3	100	PO*	Continuously for 7 days
4	200	PO*	Continuously for 7 days
5	400	PO*	Continuous from week 5 onwards
* Swallow whole with water and a meal			
During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.			
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. Vomiting: 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.			
Venetoclax is available as 10mg, 50mg and 100mg film-coated tablet. Tablets should not be chewed, crushed, or broken before swallowing			

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate bone marrow function (ANC ≥1 x 10^9 cells/L; platelet count ≥40 x 10^9 cells/L; haemoglobin ≥80 g/L),
- Creatinine clearance ≥ 30ml/min
- Adequate coagulation and hepatic function

EXCLUSIONS:

- Hypersensitivity to the active substance or to any of the excipients

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, renal and liver profile
  - Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed and pre-existing abnormalities corrected.
- Tumour burden assessment, including radiographic evaluation (i.e., CT scan to assess tumour lysis risk evaluation based on any lymph node >5cm required for all patients)
- Determination of 17p and TP53 status
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), C and HIV
  ***Hepatitis B reactivation: See Adverse events/ Regimen specific complication**

Regular tests:

Pre-dose:

- FBC, renal and hepatic profile.
- Uric acid
- These should be checked prior to each subsequent dose increase during the titration phase.

Post-dose:

- **For patients at risk of tumour lysis syndrome (TLS),**
  - FBC, renal and liver profile 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

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Dose modifications for tumour lysis syndrome (TLS):

- If 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 Supportive Care below**).
- 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.

Table 1: Dose modification of venetoclax 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.	

Haematological:

Table 2: Dose modification of venetoclax in haematological toxicity

ANC ($x10^9$/L)		**Platelets ($x10^9$/L)**	**Dose**
<1.0 with infection or fever			Withhold treatment until 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 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.
<0.5	**or**	**<25**	

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Renal and Hepatic Impairment:

Table 3: Dose modification of venetoclax in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Cr Cl (ml/min)	**Dose**	**Level**	**Dose**
≥30 -90	No dose adjustment required but patients with reduced renal function (CrCl < 80 ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS at initiation and during the dose-titration phase**).**	**Mild**	No dose adjustment is recommended.
		Moderate	A trend for increased adverse events was observed in patients with moderate hepatic impairment, these patients should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase.
<30 or patients on dialysis	Safety has not been established and a recommended dose for these patients has not been determined. Venetoclax should be administered to patients with severe renal impairment only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS.	**Severe**	A dose reduction of at least 50% throughout treatment is recommended. Patients should be monitored more closely for signs of toxicity

Management of adverse events:

Table 4: Dose Modification of venetoclax for Adverse Events

Adverse reactions	Recommended dose modification
Grade 3 or 4 Non-haematological toxicities	
First occurrence	Withhold treatment until toxicity has resolved to grade 1 or baseline level (recovery), therapy with venetoclax may be restarted at the same dose.
Second or subsequent occurrence	Withhold treatment until toxicity has resolved to grade 1 or baseline level (recovery). The dose reduction guidelines in Table 1 should be followed when resuming treatment with venetoclax. 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.

Dose modifications for use with CYP3A inhibitors

Table 5: Management of potential venetoclax interactions with CYP3A inhibitors

Inhibitors	Initiation and titration phase [a]	Steady daily dose (After titration phase)
Strong 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. **Note Azole antifungal agents are CYP3A inhibitors**. Consult the relevant SPC for further details		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to Low (**Refer to local policy).**

PREMEDICATIONS: No specific recommendations

OTHER SUPPORTIVE CARE:

- Tumour lysis prophylaxis **(Refer to local policy).**
  The prophylaxis measures listed below should be followed. More intensive measures should be employed as overall risk increases.
  - Hydration Therapy: 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.
  - Anti-hyperuricaemic agents: Should be administered 2 -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.
  - 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. Hospitalisation should be considered for subsequent dose increases based on reassessment of risk.
- Antiviral prophylaxis (**Refer to local policy).**
- PJP prophylaxis (**Refer to local policy).**
- Women of childbearing potential: Women of childbearing potential must use a highly effective method of contraception while taking venetoclax. Women should avoid becoming pregnant while taking venetoclax and for at least 30 days after ending 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.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Tumour Lysis Syndrome (TLS):** 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. 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. The prophylaxis measures listed above under Supportive Care should be followed. More intensive measures should be employed as overall risk increases.
- **Neutropenia:** Grade 3 or 4 neutropenia has been reported in patients treated with venetoclax.

Complete blood counts should be monitored throughout the treatment period. Dose interruptions or reductions are recommended for patients with severe neutropenia. Serious infections, including sepsis with fatal outcome, have been reported. Monitoring of any signs and symptoms of infection is required. Suspected infections are to receive prompt treatment, including antimicrobials and dose interruption or reduction as appropriate.

- **Immunisation:** The safety and efficacy of immunisation with live attenuated vaccines during or following venetoclax therapy have not been studied. Live vaccines should not be administered during treatment and thereafter until B-cell recovery.
- **Hepatitis B Reactivation:**
- Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- **Concomitant use of venetoclax with strong CYP3A inhibitors:** At initiation and during the dose-titration phase is contraindicated due to increased risk for TLS. For patients who have completed the dose-titration phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced 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 moderate CYP3A inhibitors:** 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 dose of venetoclax and the doses for the titration phase should be reduced by at least 50%. Patients should be monitored more closely for signs and symptoms of TLS. For patients who have completed the dose-titration phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced by 50% when used concomitantly with moderate 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
- Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax as they contain inhibitors of CYP3A.
- **Concomitant use of venetoclax with P-gp and BCRP inhibitors:** At initiation and during the dose-titration phase should be avoided; if a P-gp and BCRP inhibitor must be used, patients should be monitored closely for signs of toxicities.
- **Concomitant use of venetoclax with strong or moderate CYP3A inducers**: Should be avoided. Alternative treatments with less CYP3A induction should be considered as venetoclax efficacy may be reduced. Preparations containing St. John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced
- **Co-administration of bile acid sequestrants with venetoclax**: Should be avoided as this may reduce the absorption of venetoclax. If co-administration is necessary the SmPC for the bile acid sequestrant should be followed to reduce the risk for an interaction, and venetoclax should be administered at least 4-6 hours after the sequestrant.
- **Co-administration of narrow therapeutic index P-gp, or BCRP substrates with Venetoclax**: Should be avoided. If co-administration is necessary it should be used in caution.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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3. Venclyxto®(Venetoclax) SmPC Accessed October 2020 Available at https://www.ema.europa.eu/en/documents/product-information/venclyxto-epar-product-information_en.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	15/10/2018		Dr Patrick Thornton
2	07/08/2019	Updated recommended dose modification in hepatic impairment as per SmPC update Updated emetogenic potential	Dr Patrick Thornton
3	03/03/2021	Regimen review Addition of table for Dose modifications for use with CYP3A inhibitors as per SmPC update Updated adverse events/regimen specific complications with regard to serious infections and management of hepatitis B reactivation	Dr Patrick Thornton

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.