Venetoclax and obinutuzumab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
In combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)	C91	00715a	Venetoclax: CDS 01/03/2022 Obinutuzumab: ODMS 01/03/2022

* This is for post 2012 indications only

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 commencing on Day 22 of Cycle 1 with a starting dose of 20 mg. This is increased every 7 days over a period of 5 weeks up to a daily dose of 400 mg as shown in Table 1. The 5-week dose-titration schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of tumour lysis syndrome (TLS). Venetoclax is given for a total of 12 cycles or until disease progression or unacceptable toxicities. Each cycle is 28 days.

Obinutuzumab is administered at a dose of 100 mg on Cycle 1 Day 1, followed by 900 mg which may be administered on Day 1 or Day 2, followed by 1000 mg on Days 8 and 15 of Cycle 1. From Cycles 2-6, obinutuzumab is administered at a dose of 1000 mg on Day 1 of each cycle for a total of 6 cycles or until disease progression or unacceptable toxicities. Each cycle is 28 days.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Table 1: Dose titration schedule

WEEK	Venetoclax Dose (mg) [a, b, c]	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	Continuously for 7 days
[a] Swallow tablets whole with water and with a meal, at approximately the same time each day. Tablets should not be chewed, crushed, or broken before swallowing.			
[b] During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.			
[c] 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.			

Table 2: Treatment of venetoclax and obinutuzumab

Day	Drug	Dose	Route	Diluent and rate	Cycle
1	Obinutuzumab [a, b]	100mg	IV infusion	100mL of 0.9% NaCl. Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.	1
2 (or day 1 continued)	Obinutuzumab	900mg	IV infusion	250mL 0.9% NaCl. If no infusion related reaction (IRR) during the previous infusion, administer at 50 mg/hour. [c] If the patient experienced an IRR during the previous infusion, start with administration at 25 mg/hour. [c]	1
8,15	Obinutuzumab	1000mg	IV infusion	250mL 0.9% NaCl at a maximum rate of 400mg/hour. [d, e]	1
22-28	Venetoclax	See Table 1	PO*	N/A	1
1	Obinutuzumab	1000mg	IV infusion	250mL 0.9% NaCl at a maximum rate of 400mg/hour. [d, e]	2-6
1-28	Venetoclax	See Table 1	PO*	N/A	2
1-28	Venetoclax	400mg	PO	N/A	3-12
[a] If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for obinutuzumab should be maintained between doses.					
[b] Obinutuzumab infusions should NOT be administered as an intravenous push or bolus.					
[c] The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.					
[d] If no IRR during the prior infusion when final infusion rate was 100mg/hour or faster, infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.					
[e] If the patient experienced an IRR during the previous infusion, administer at 50 mg/hour. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.					
*See Table 1 for administration of venetoclax.					

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indication as above
- ≥ 18 years
- Adequate bone marrow function
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to venetoclax, obinutuzumab, humanized or murine monoclonal antibodies/murine products or to any of the excipients
- Pregnancy/breastfeeding

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).
  - Please refer to **Table 9** in the Supportive Care section for **recommended TLS prophylaxis** and monitoring, based on tumour burden, during venetoclax treatment.
- Cardiac function if clinically indicated
- Uric acid
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), C and HIV

*Hepatitis B reactivation: Regimen Specific Complication

Regular tests:

- **Pre-dose of venetoclax:**
  - FBC, renal and liver profile
  - Uric acid
  - These should be checked prior to each subsequent dose increase during the venetoclax titration phase.

- **Post-dose of venetoclax:**

For all 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 at subsequent dose increases.

For obinutuzumab:

- FBC, renal and liver profile and LDH prior to each cycle
- ECG as clinically indicated

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.
- No dose reductions are recommended for obinutuzumab.

Dose modifications for tumour lysis syndrome (TLS):

- If patient experiences blood chemistry changes or symptoms 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 3). 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.
- Consider discontinuing venetoclax for patients who require dose reductions to less than 100mg for more than 2 weeks.

Table 3: Dose modification of venetoclax 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.	

Haematological:

Table 4: 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 3 should be followed when resuming treatment with venetoclax following resolution. A larger dose reduction may occur at the discretion of the physician.
<0.5	Or	<25	
To reduce the infection risks associated with neutropenia, consider use of granulocyte-colony stimulating factor (G-CSF) as clinically needed.			
Consider discontinuing venetoclax for patients who require dose reductions to less than 100mg for more than 2 weeks.			

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

Renal and Hepatic Impairment:

Table 5: Dose modification of venetoclax and obinutuzumab in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment	
Venetoclax [a]	**CrCl (mL/min)**	**Dose**	**Level**	**Dose**
	≥ 15	No dose adjustment is needed.	**Child-Pugh A/B and mild/moderate:**	No dose adjustment is needed
	< 15	No need for dose adjustment is expected. Monitor closely due to increased risk of TLS.	**Child-Pugh C and severe:**	50% of the original dose
	Haemodialysis	No need for dose adjustment is expected. Monitor closely due to increased risk of TLS.		
Obinutuzumab [b]	**Renal Impairment:**	No dose adjustment is needed	**Hepatic impairment:**	No need for dose adjustment is expected
	Haemodialysis:	No dose adjustment is expected		

[a] Venetoclax (renal and hepatic - Giraud et al 2023)

[b] Obinutuzumab (renal and hepatic - Giraud et al 2023)

Management of adverse events:

Table 6: Dose modifications of venetoclax and obinutuzumab for adverse events

Drug	Adverse reaction*	Recommended dose modification
Venetoclax	**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 3 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.
Obinutuzumab	**Infusion Related Reactions (IRR)**	
	Grade 1-2	Reduce infusion rate and treat symptoms. Infusion can be continued upon symptom resolution and if patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Treatment Table). The Day 1 (Cycle 1) infusion rate may be increased back up to 25mg/hour after 1 hour, but not increased further.
	Grade 3 First occurrence	Temporarily stop the infusion and treat the symptoms. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Treatment Table). The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hour after 1 hour, but not increased further.
	Grade 3 Second occurrence	Stop infusion and discontinue treatment.
	Grade 4	Stop infusion and discontinue treatment.
	Progressive multifocal leukoencephalopathy (PML)	Discontinue treatment
	Hypersensitivity	Discontinue treatment

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

Dose modifications for use with CYP3A inhibitors:

Table 7: Management of potential venetoclax interactions with CYP3A inhibitors in CLL

Inhibitors	Initiation and titration phase[a]	Steady daily dose (After titration phase)
Strong CYP3A inhibitor	Contraindicated	Reduce the venetoclax dose to 100mg or less (or by at least 75% if already modified for other reasons)
Moderate CYP3A inhibitor [a]	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:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting- Available on the NCCP website :

Venetoclax: Minimal to low **(Refer to local policy)**
Obinutuzumab: Minimal **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

Table 8: Premedication to be administered before obinutuzumab infusion to reduce the risk of IRRs

Day of treatment cycle	Patients requiring premedication	Premedication	Administration
Cycle 1: **Day 1 and Day 2**	All patients	Intravenous corticosteroid [a]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral analgesic/anti-pyretic [b]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic medicine [c]	
Cycle 1: **Day 8 and Day 15** **Cycles 2-6:** **Day 1**	Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x 10^9 /L prior to next treatment	Intravenous corticosteroid [a]	Completed at least 1 hour prior to obinutuzumab infusion
	All patients	Oral analgesic/anti-pyretic [b]	At least 30 minutes before obinutuzumab infusion

	Patients with an IRR (Grade 1 or more) with the previous infusion	Anti-histaminic medicine [c]	

[a]100 mg predniSONE/prednisoLONE or 20 mg dexAMETHasone or 80 mg methylPREDNISolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
[b]e.g. 1000 mg paracetamol
[c]e.g. 10mg chlorphenamine

OTHER SUPPORTIVE CARE:

- **Tumour lysis prophylaxis** (TLS)

Table 9 below describes the recommended TLS prophylaxis and monitoring during venetoclax treatment.

Table 9: Recommended TLS prophylaxis based on tumour burden in patients with CLL

Tumour burden		**Prophylaxis**		**Blood chemistry monitoring** [c, d]
		Hydration [a]	**Anti-hyperuricaemics** [b]	**Setting and frequency of assessments**
Low	All LN <5cm AND ALC < $25x10^9$/L	Oral (1.5-2 L)	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose
Medium	All LN 5cm to <10cm OR ALC ≥ $25x10^9$/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalisation for patients with CrCl <80mL/min; see below for monitoring in hospital
High	All LN ≥10cm OR ALC ≥ $25x10^9$/L AND Any LN ≥5cm	Oral (1.5-2 L) and intravenous (150-200 mL/hour as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent dose increases: Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node.
[a] Instruct patients to drink water daily starting 2 days before and throughout the dose-titration phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b] Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.
[c] Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d] At subsequent dose increases, monitor blood chemistries at 6 to 8 hours and at 24 hours for patients who continue to be at risk of TLS.

- 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:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS

- **Tumour Lysis Syndrome (TLS):** Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS at initiation and during the 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. All patients should be assessed for risk and should receive appropriate prophylaxis measures listed under supportive care should be followed. More intensive measures should be employed as overall risk increases. With obinutuzumab, there is an increased risk with high tumour burden and/or a high circulating lymphocyte count (>25x10^9/L) and/or renal impairment (CrCl < 70ml/min).
- **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:

- Current SmPC and drug interaction databases should be consulted for information.

COMPANY SUPPORT RESOURCES / useful links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Venetoclax Patient Alert Card:
https://www.hpra.ie/img/uploaded/swedocuments/207b83cf-0464-44de-8d67-a2166c774583.pdf

REFERENCES:

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2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
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5. Obinutuzumab (Gazyvaro®) Summary of Product Characteristics. Last updated: 20/11/2023. Accessed Jan 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/gazyvaro-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	28/02/2022		Dr Derville O'Shea
2	04/06/2024	Regimen reviewed. - Added extra detail to Table 2 to align with SmPC (Table 4). - Updated dose modification in renal and hepatic impairment to align with Giraud et al (2023) - Aligned Table 7 to SmPC. - Updated anti-histamine example in Table 8. - Updated ADVERSE EFFECTS and DRUG INTERACTIONS sections to align with NCCP Standardisation. - Separated REGIMEN SPECIFIC COMPLICATIONS section. - NCCP Standardisation	Dr Derville O'Shea
2a	27/11/2024	Updated emetogenic potential section with standard wording.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.