Venetoclax and obinutuzumab Therapy

INDICATIONS FOR USE:

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

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 20mg. 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 900mg which may be administered on Day 1 or Day 2, followed by 1000mg on Days 8 and 15 of Cycle 1. From Cycles 2-6, obinutuzumab is administered at a dose of 1,000mg 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 therapy is administered.

Table 1: Dose titration schedule

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	Continuously for 7 days
Swallow tablets whole with water and with a meal, at approximately the same time each day.			
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.			

Table 2: Treatment of venetoclax and obinutuzumab

Day	Drug	Dose	Route	Diluent and rate	Cycle
1	Obinutuzumab	100mg	IV infusion	100ml of 0.9% NaCl. Administer at 25 mg/hr 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 reaction during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.	**1**
8,15	Obinutuzumab	1000mg	IV infusion	If no infusion reaction during the prior infusion when final infusion rate was 100mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.	**1**
22-28	Venetoclax	See Table 1	PO*	N/A	**1**
1	Obinutuzumab	1000mg	IV infusion	250ml 0.9% NaCl. Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.	**2-6**
1-28	Venetoclax	See Table 1	PO*	N/A	**2**
1-28	Venetoclax	400mg	PO	N/A	**3-12**
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.					
Obinutuzumab infusions should NOT be administered as an intravenous push or bolus.					
*See Table 1 for administration of venetoclax.					

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: See Adverse events/ 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 of 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. 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	

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Renal and Hepatic Impairment:

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

Drug	Renal impairment		Hepatic impairment	
Venetoclax	**CrCl (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 / Moderate**	No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Patients with moderate hepatic impairment 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.
Obinutuzumab	**CrCl (ml/min)**	**Dose**	Safety and efficacy not established in patients with impaired hepatic function. No specific dose recommendations can be made.	
	30-89	100%		
	<30	Safety and efficacy not established		

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/hr 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/hr 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

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Dose modifications for use with CYP3A inhibitors:

Table 7: 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:

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

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 2	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic medicine[3]	
Cycle 1: Day 8, 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[1]	Completed at least 1 hour prior to obinutuzumab infusion
	All patients	Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1 or more) with the previous infusion	Anti-histaminic medicine[3]	
[1]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. *[2]e.g. 1000 mg paracetamol* *[3]e.g. 50 mg diphenhydramine*			

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/hr 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 / REGIMEN SPECIFIC COMPLICATIONS:

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

- **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.
- **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).
- **Neutropenia:** Grade 3 or 4 neutropenia has been reported in patients treated with venetoclax in combination with obinutuzumab. Complete blood counts should be monitored throughout the treatment. 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. Severe and life threatening neutropenia including febrile neutropenia has been reported during treatment with obinutuzumab. Consider G-CSF, if severe and associated with infection; consider anti-microbial prophylaxis if severe and prolonged (>1 week), including anti-viral and anti-fungal prophylaxis. Cases of late onset neutropenia (occurring >28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia. Dose delays may be required.

Venetoclax:

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

- **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.
- **Obinutuzumab**: **Infusion Related Reactions:** These are minimised by administering Day 1 obinutuzumab over 2 days in combination with pre-medications, as outlined in Table 9. Most reactions are mild or moderate and are further reduced by slowing or temporarily stopping the infusion. Risks for IRRs include high tumour burden, renal impairment and Cumulative Illness Rating Scale (CIRS) >6. If the patient experiences an IRR, the infusion should be managed according to the grade of the reaction (see Table 7).
- **Hypotension:** As a symptom of IRRs, hypotension may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits

and risks of withholding their anti-hypertensive medicine.

- **Worsening of pre-existing cardiac conditions:** Atrial fibrillation, angina, acute coronary syndrome, myocardial infarction, hypertension and heart failure can occur in patients with underlying cardiac disease. Monitor closely and hydrate cautiously to prevent fluid overload.
- **Thrombocytopenia:** This can be severe and life-threatening, including acute onset within 24 hours post infusion; monitor closely and treat bleeding according to best practice. Renal impairment increases risk of thrombocytopenia. Dose delays may be required. Use of all concomitant therapies that could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.
- **Progressive multifocal leukoencephalopathy (PML):** New or worsening neurological, cognitive or behavioural symptoms or signs due to PML have occurred with obinutuzumab.

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.
- No interaction studies have been performed with obinutuzumab.

- Vaccinations with live organism vaccines are not recommended.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	28/02/2022		Dr Derville O'Shea

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