Venetoclax and riTUXimab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Venetoclax in combination with riTUXimab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy	C91	00575a	Venetoclax: CDS 01/07/2020 riTUXimab: N/A

* 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 patient 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 maintenance dose of 400mg is reached as demonstrated 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).

The recommended dose of venetoclax in combination with riTUXimab is 400 mg once daily.
riTUXimab should be administered after the patient has completed the venetoclax dose-titration schedule and has received the daily dose of 400 mg venetoclax for 7 days.

- riTUXimab should be administered on Day 1 Cycle 1 (375mg/m^2) and then every 28 days at 500mg/m^2 for Cycles 2-6.
- Venetoclax should be taken for 24 months from Day 1 Cycle 1 of riTUXimab until disease progression or unacceptable toxicity develops.

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

Table 1: Dose titration schedule of venetoclax

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. Tablets should not be chewed, crushed, or broken before swallowing.			
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.			

Table 2: Treatment of venetoclax and riTUXimab

Day	Drug	Dose	Route	Diluent & Rate	Cycle (28 days)
1	**riTUXimab**	375 mg/m^2	IV infusion[1] Observe post infusion[1]	500ml NaCl 0.9% at a maximum rate of 400mg/hr[1]	Cycle 1 only
1-28	**Venetoclax**	400mg	PO[2]		Cycle 1-24
1	**riTUXimab**	500mg/m^2	IV infusion[1] Observe post infusion[1]	500ml NaCl 0.9% at a maximum rate of 400mg/hr[1]	Cycle 2-6
[1] See Table 3: Guidance for administration of riTUXimab.					
[2] See Table 1 for administration of venetoclax.					

Table 3: Guidance for Administration of riTUXimab

The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Subsequent infusions can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr. Development of an allergic reaction may require a slower infusion rate. See Hypersensitivity/Infusion reactions under Adverse Effects/Regimen Specific Complications below. Any deviation from the advised infusion rate should be noted in local policies.
Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies
riTUXimab should be diluted to a final concentration of 1-4mg/ml.
Rapid rate infusion schedule[i] **See NCCP guidance Available on the NCCP website .** If patients did **not** experience a serious infusion related reaction with their first or subsequent infusions of a dose of riTUXimab administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions. Initiate at a rate of 20% of the total dose for the first 30 minutes and then 80% of the dose for the next 60 minutes (total infusion time of 90 minutes). If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions. Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to riTUXimab, should not be administered the more rapid infusion.

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Diagnosis of relapsed or refractory chronic lymphocytic leukaemia by a validated CLL diagnostic criteria
    - Relapsed disease: A patient who previously achieved a CR or PR but after a period of 6 months or more demonstrates evidence of progression
    - Refractory disease: Treatment failure or disease progression within 6 months after the last anti-leukaemia therapy
- Adequate organ function (renal, hepatic)
- Consider growth factor and transfusion support for disease related cytopenias

EXCLUSIONS:

- Hypersensitivity to venetoclax, riTUXimab or to any of the excipients
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Patients in a severely immunocompromised state

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 10 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, SPEP, DAT
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), C and HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

Pre-dose of venetoclax:

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

Post-dose of venetoclax:

- **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.

For riTUXimab:

- FBC, renal and liver profile
- LDH
- Cardiac function if 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 modifications of riTUXimab are recommended.

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 4). 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 4: 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 5: 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 4 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 6: Dose modification of venetoclax and riTUXimab in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
	CrCl (ml/min)	Dose	Level	Dose
Venetoclax	≥ 15 ml/min	No dose adjustment is needed.	**Child-Pugh A/B and Mild/moderate**	No dose adjustment is needed
	< 15 ml/min	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		
riTUXimab	Renal impairment: No need for dose adjustment is expected Haemodialysis: No dose adjustment is needed		Hepatic impairment: No need for dose adjustment is expected	

Management of adverse events:

Table 7: Dose Modification for Adverse Events

Drug	Adverse reactions*	Recommended dose modification
Venetoclax	**Grade 3 or 4 Non-hematological 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 4 should be followed when resuming treatment with venetoclax[1]. A larger dose reduction may occur at the discretion of the physician.
riTUXimab	Severe infusion related reaction (e.g. dyspnoea, bronchospasm, hypotension or hypoxia)	
	First occurrence	Interrupt infusion immediately. Evaluate for cytokine release/tumour lysis syndrome (appropriate laboratory tests) and pulmonary infiltration (chest x-ray). Infusion may be restarted on resolution of all symptoms, normalisation of laboratory values and chest x-ray findings at no more than one-half the previous rate.
	Second occurrence	Consider discontinuing treatment. Consider coverage with steroids for those who are not already receiving steroids.
	Mild or moderate infusion-related reaction	Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms
[1]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

Dose modifications for use with CYP3A inhibitors

Table 8: 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:

- 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)**
riTUXimab: 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:

Premedication consisting of an anti-pyretic and an antihistamine should always be administered before each infusion of riTUXimab. Consider the inclusion of a glucocorticoid in patients not receiving glucocorticoid containing chemotherapy.

Table 9: Suggested pre-medications prior to riTUXimab infusion

Drugs	Dose	Route
Paracetamol	1g	PO 60 minutes prior to riTUXimab infusion
Chlorphenamine	10mg	IV bolus 60 minutes prior to riTUXimab infusion
Hydrocortisone	100mg	IV bolus 60 minutes prior to riTUXimab infusion

OTHER SUPPORTIVE CARE:

- Tumor lysis syndrome (TLS) prophylaxis **(Refer to local policy).**

  Table 10 below describes the recommended TLS prophylaxis and monitoring during venetoclax treatment.

Table 10: 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	Any 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	Any 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.

Venetoclax is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions

- **Neutropenia:** Grade 3 or 4 neutropenia has been reported in patients treated with venetoclax in combination with riTUXimab. 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, dose interruption or reduction and use of growth factors as appropriate.

- **Immunisation:** The safety and efficacy of immunisation with live attenuated vaccines during or following venetoclax or riTUXimab 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.

Venetoclax

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 appropriate prophylaxic measures listed under supportive care should be followed. More intensive measures should be employed as overall risk increases.

riTUXimab

- **Hypersensitivity/Infusion Reactions**: Close monitoring is required throughout the first infusion. (Refer to local policy). riTUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, pruritis, sneezing, cough, fever or faintness.
- **Severe Cytokine Release syndrome:** Usually occurs within 1 to 2 hours of initiating the first infusion. This syndrome may be associated with some features of cytokine release/tumor lysis syndrome such as hyperuricemia, hyperkaliemia, hypocalcemia, hyperphosphatemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death.
    - Pulmonary interstitial infiltrates or oedema visible on chest x-ray may accompany acute respiratory failure.
    - For severe reactions, stop the infusion immediately and evaluate for tumor lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized.
- **Cardiac Disorders**: Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.
- **Infections:** riTUXimab should not be administered to patients with an active, severe infection. Caution should be exercised when considering the use of riTUXimab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis.
- **Severe Mucocutaneous Reactions**: These include Steven Johnson syndrome and toxic epidermal necrolysis. Discontinue in patients who develop a severe mucocutaneous reaction. The safety of readministration has not been determined.
- **Progressive multifocal leukoencephalopathy (PML**): Use of riTUXimab may be associated with an increased risk of PML. If a patient develops PML, the dosing of riTUXimab must be permanently discontinued.

DRUG INTERACTIONS:

- **Concomitant use of venetoclax with strong and moderate CYP3A inhibitors:** Refer to Table 8 for guidelines on the management of potential venetoclax interactions with 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.
- **Antihypertensives**: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- **Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres** may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	27/07/2020		NCCP Lymphoid Clinical Advisory Group
2	07/02/2024	Reviewed. Updated treatment table footnotes, baseline tests and exclusions. Updated dose modification for TLS wording. Updated Table 5. Addition of riTUXimab to Table 6. Updated Table 6 to align with recommendations of Giraud et al. Addition of Table 8 (Dose modifications for use with CYP3A inhibitors) and Table 10 (Recommended TLS prophylaxis based on tumour burden in patients with CLL) as per SmPC update. Updated adverse events / regimen specific complications and drug interactions.	Dr Patrick Thornton
2a	27/11/2024	Updated emetogenic potential section with standard wording.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The rapid infusion is an unlicensed means of administration of riTUXimab for the indications described above, in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.