Venetoclax and rituximab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Venetoclax in combination with riTUXimab is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy	C91	00575a	Venetoclax: CDS 01/07/2020 RiTUXimab: Hospital

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 Cycle 1 Day 1 of riTUXimab until disease progression or unacceptable toxicity develops.

Recommended that facilities to treat anaphylaxis MUST be present when therapy 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			
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 riTUXimab

Day	Drug	Dose	Route	Diluent & Rate	Cycle (28 days)
1	**riTUXimab**	375 mg/m^2	IV infusion[1] Observe post infusion[2]	500ml NaCl 0.9% at a maximum rate of 400mg/hr.[1,3,4]	Cycle 1 only
1-28	**Venetoclax**	400mg	PO*		Cycle 1-24
1	**riTUXimab**	500mg/m^2	IV infusion[1] Observe post infusion[2]	500ml NaCl 0.9% at a maximum rate of 400mg/hr [1,3,4]	Cycle 2-6

[1]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

[2]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.

[3]RiTUXimab should be diluted to a final concentration of 1-4mg/ml.

[4]**Rapid rate infusion schedule[I] See NCCP guidance here**
If patients did **not** experience a serious infusion related reaction with their first or subsequent infusions of a dose of riTUXmab 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 reactions to any prior biologic therapy or to riTUXimab, should not be administered the more rapid infusion.

*See table 1 for administration of venetoclax

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 the active substance 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)
- 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 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 3: 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
The modified dose should be continued for 1 week before increasing the dose.	

Hematological:

Table 4: Dose modification of venetoclax in hematological 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 5: Dose modification of venetoclax in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
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**	No dose adjustment is recommended.
		Moderate	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 establishedand 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 for patients with severe hepatic impairment. These patients should be monitored more closely for signs of toxicity.

Management of adverse events:

Table 6: 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 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.
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

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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Venetoclax**:** Minimal to Low (**Refer to local policy)**
RiTUXimab: Minimal (**Refer to local policy)**

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 7: Suggested pre-medications prior to riTUXimab infusion:

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

OTHER SUPPORTIVE CARE:

- Tumor 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. ***Venetoclax 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.
- **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 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. Supportive measures including antimicrobials for any signs of infection should be considered.

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 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.

- **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.

ATC CODE:

Venetoclax - L01XX52
RiTUXimab - L01XC02

REFERENCES:

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4. NCCP | RiTUXimab Rapid Infusion Rate Guidance | V2 2019 available at https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/guidance%20on%20rituximab%20rapid%20infusion%20rate.pdf
5. Rituximab (Mabthera®) Summary of Product Characteristics. Last updated: 25Mar2020. Accessed Apr 2020 available at https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	27/07/2020		NCCP Lymphoid Clinical Advisory Group

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 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.