Regimen Reference Order – CLL– venetoclax + riTUXimab

ARIA: CLL - [venetoclax + riTUXimab (ramp-up)]
CLL - [venetoclax + riTUXimab (post ramp-up)]

Planned Course: **venetoclax ramp-up once daily until ramp-up complete**
Once ramp-up complete: riTUXimab every 28 days for 6 doses and venetoclax once daily for 2 years

Indication for Use: **Chronic Lymphocytic Leukemia Relapsed/Refractory**

CVAD: At Provider's Discretion

Proceed with treatment if:

- ***ANC equal to or greater than 1 x 10^9/L AND Platelets equal to or greater than 30 x 10^9/L***
- ***Potassium is within normal range (3.5 to 5 mmol/L)***
- ***Corrected calcium is within normal range (2.2 to 2.6 mmol/L)***
- ***Phosphate is within normal range (1 to 1.5 mmol/L)***
- ***Uric acid is less than 420 micromol/L or less than baseline****
- ***Serum creatinine is normal or increase is less than 20 micromol/L above baseline****
- ***LDH normal or less than 1.5 times baseline****

*** Baseline: defined as the value before treatment initiation***

❖ **Contact treating Hematologist if parameters not met**

SEQUENCE OF MEDICATION ADMINISTRATION

Pre-treatment Requirements

Drug	Dose	CCMB Administration Guideline
Patient to drink 1.75 litres of water per day: • Starting two days prior to starting venetoclax until 24 hours after first dose of venetoclax • Starting two days prior to until 24 hours after each venetoclax dose escalation (i.e. as part of the "ramp-up" dosing schedule) ***Alert:** Contact physician if patient did not follow hydration as directed*		
allopurinol	300 mg	Orally once daily to begin 3 days prior to venetoclax initiation and **MUST** continue until venetoclax dose escalation is complete and patient is directed to discontinue **(Self-administered at home)** ***Alert:** Contact physician if patient did not take allopurinol as directed*

Treatment Regimen – CLL– venetoclax and riTUXimab

Drug	Dose	CCMB Administration Guideline
Dose Escalation (venetoclax "ramp-up" dosing - usually 5 weeks duration) – self-administered at home		
Dose Level 1 (Usual duration = 7 days)		
venetoclax	20 mg (2 of 10 mg tablets) **Day 1**	Orally once daily with food at 6:00 a.m. (Swallow whole) ***Alert:** Post-dose biochemistry must be drawn 6 to 8 hours following first dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 2 dose without confirmation of blood work*
	20 mg (2 of 10 mg tablets) **Day 2**	Orally once daily with food at 6:00 a.m. (Swallow whole) ***Alert:** Post-dose biochemistry must be drawn 6 – 8 hours following Day 2 dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 3 dose without confirmation of blood work*
	20 mg (2 of 10 mg tablets) **Days 3 to 7**	Orally once daily with food at 6:00 a.m. (Swallow whole)
Dose Level 2* (Usual duration = 7 days) * Only proceed with dose increase as per prescriber's assessment of blood work, tumor lysis and tolerance during Dose Level 1. In some cases, the dose may remain at Dose Level 1 for more than a week, until safe to escalate		
venetoclax	50 mg (1 of 50 mg tablet) **Day 1**	Orally once daily with food at 6:00 a.m. (Swallow whole) ***Alert:** Post-dose biochemistry must be drawn 6 – 8 hours following first dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 2 dose without confirmation of blood work*
	50 mg (1 of 50 mg tablet) **Day 2**	Orally once daily with food at 6:00 a.m. (Swallow whole) ***Alert:** Post-dose biochemistry must be drawn 6 – 8 hours following Day 2 dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 3 dose without confirmation of blood work*
	50 mg (1 of 50 mg tablet) **Days 3 to 7**	Orally once daily with food at 6:00 a.m. (Swallow whole)
Dose Level 3* (Usual duration = 7 days) * Only proceed with dose increase as per prescriber's assessment of blood work, tumor lysis and tolerance during		

Dose Level 2. In some cases, the dose may remain at Dose Level 2 for more than a week, until safe to escalate		
venetoclax	100 mg (1 of 100 mg tablet) **Day 1**	Orally once daily with food at 6:00 a.m. (Swallow whole) ***Alert:** Post-dose biochemistry must be drawn 6 – 8 hours following first dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 2 dose without confirmation of blood work*
	100 mg (1 of 100 mg tablet) **Day 2**	Orally once daily with food at 6:00 a.m. (Swallow whole) ***Alert:** Post-dose biochemistry must be drawn 6 – 8 hours following Day 2 dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 3 dose without confirmation of blood work*
	100 mg (1 of 100 mg tablet) **Days 3 to 7**	Orally once daily with food at 6:00 a.m. (Swallow whole)
Dose Level 4* (Usual duration = 7 days) * Only proceed with dose increase as per prescriber's assessment of blood work, tumor lysis and tolerance during Dose Level 3. In some cases, the dose may remain at Dose Level 3 for more than a week, until safe to escalate		
venetoclax	200 mg (2 of 100 mg tablets) **Day 1**	Orally once daily with food at 6:00 a.m. (Swallow whole) **Alert: Post-dose biochemistry must be drawn 6 – 8 hours following first dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 2 dose without confirmation of blood work*
	200 mg (2 of 100 mg tablets) **Day 2**	Orally once daily with food at 6:00 a.m. (Swallow whole) **Alert: Post-dose biochemistry must be drawn 6 – 8 hours following Day 2 dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 3 dose without confirmation of blood work*
	200 mg (2 of 100 mg tablets) **Days 3 to 7**	Orally once daily with food at 6:00 a.m. (Swallow whole)
Dose Level 5* (Usual duration = 7 days) * Only proceed with dose increase as per prescriber's assessment of blood work, tumor lysis and tolerance during Dose Level 4. In some cases, the dose may remain at Dose Level 4 for more than a week, until safe to escalate		
venetoclax	400 mg (4 of 100 mg tablets) **Day 1**	Orally once daily with food at 6:00 a.m. (Swallow whole) ***Alert:** Post-dose biochemistry must be drawn 6 – 8 hours following first dose*

		Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed *Do not proceed to Day 2 dose without confirmation of blood work*
	400 mg (4 of 100 mg tablets) **Day 2**	Orally once daily with food at 6:00 a.m. (Swallow whole) ***Alert:** Post-dose biochemistry must be drawn 6 – 8 hours following Day 2 dose* *Patient must stay at CancerCare Manitoba until biochemistry results available and reviewed* *Do not proceed to Day 3 dose without confirmation of blood work*
	400 mg (4 of 100 mg tablets) **Days 3 to 7**	Orally once daily with food at 6:00 a.m. (Swallow whole)
venetoclax + riTUXimab (Cycles 1 to 6) **riTUXimab should start 7 days after maximum dose of venetoclax is achieved (as per prescriber's assessment)**		
Establish primary solution 500 mL of: normal saline		
Cycle 1		
Drug	**Dose**	**CCMB Administration Guideline**
cetirizine	10 mg	Orally 30 minutes prior to riTUXimab
acetaminophen	650 mg	Orally 30 minutes prior to riTUXimab
dexamethasone	40 mg	IV in normal saline 50 mL over 15 minutes
riTUXimab (IV brand name specific)	375 mg/m^2	**Slow infusion:** IV made up to a final concentration of 1 mg/mL in normal saline. Start at 50 mg/hr for 60 minutes and escalate infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr **Nursing Alert: IV tubing is primed with riTUXimab* **Alert: Ensure brand name on prescription label (indicated in brackets on prescription label) matches prescribed order* **Alert: Pharmacy to ensure final volume on label*
venetoclax	400 mg (4 of 100 mg tablets)	Orally once daily with food (Swallow whole) on Days 1 to 28 **(Self-administered at home)**
Cycles 2 to 6 (SUBCUTANEOUS riTUXimab)		
cetirizine	10 mg	Orally 30 minutes prior to riTUXimab
acetaminophen	650 mg	Orally 30 minutes prior to riTUXimab
dexamethasone	12 mg	Orally 30 minutes prior to riTUXimab
riTUXimab	1600 mg (1600 mg = 13.4 mL)	**Subcutaneous**: Administer over 7 minutes into abdomen Syringe should be held in hand for 5 minutes to warm up and decrease viscosity

		Use 25G needle **Nursing Alert: Ensure subcutaneous riTUXimab formulation is used (riTUXimab-hyaluronidase, human)*
venetoclax	400 mg (4 of 100 mg tablets)	Orally once daily with food (Swallow whole) on Days 1 to 28 **(Self-administered at home)**
OR		
Cycles 2 to 6 (INTRAVENOUS riTUXimab)		
cetirizine	10 mg	Orally 30 minutes prior to riTUXimab
acetaminophen	650 mg	Orally 30 minutes prior to riTUXimab
dexamethasone	12 mg	IV in normal saline 50 mL over 15 minutes
riTUXimab (IV brand name specific)	500 mg/m^2	**Slow infusion**: IV made up to a final concentration of 1 mg/mL in normal saline. Start at 100 mg/hr for 30 minutes and escalate infusion rate in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr **Nursing Alert: IV tubing is primed with riTUXimab* **Alert: Ensure brand name on prescription label (indicated in brackets on prescription label) matches prescribed order* **Alert: Pharmacy to ensure final volume on label* **OR** **Rapid Infusion**: IV in normal saline over 90 minutes: Infuse 50 mL of a 250 mL bag (or 100 mL of a 500 mL bag) over 30 minutes, then infuse the remaining 200 mL (or 400 mL of a 500 mL bag) over 60 minutes *Concentration dependent drug. Pharmacy will adjust diluent volume to ensure drug stability* **Alert: Ensure brand name on prescription label (indicated in brackets on prescription label) matches prescribed order* **Alert: Pharmacy to ensure final volume on label*
venetoclax	400 mg (4 of 100 mg tablets)	Orally once daily with food (Swallow whole) on Days 1 to 28 **(Self-administered at home)**
Cycles 7 to 26 (venetoclax)		
venetoclax	400 mg (4 of 100 mg tablets)	Orally once daily with food (Swallow whole) on Days 1 to 28 **(Self-administered at home)**
venetoclax (Venclexta ®) available dosage strengths: 10 mg, 50 mg and 100 mg tablets **Classification: Cytotoxic, Hazardous**		

In the event of an infusion-related hypersensitivity reaction, refer to the **'Hypersensitivity Reaction Standing Order'**

REQUIRED MONITORING

Dose Escalation ("ramp-up")
Every Dose Level

- CBC, serum creatinine, potassium, phosphate, calcium, albumin, liver enzymes, LDH and uric acid as per Physician Orders
    - At baseline (Day 0), then
    - 6 to 8 hours post drug (Day 1 of Dose Level), then
    - 6 to 8 hours post drug (Day 2 of Dose Level), then
    - As per Physician Orders, to determine ongoing dose of venetoclax

Post Dose Escalation (post "ramp-up")

- CBC, serum creatinine, potassium, phosphate, calcium, albumin, liver enzymes, LDH and uric acid as per Physician Orders
    - Monthly for Cycles 1 to 6, then
    - Every three months once stable

INTRAVENOUS riTUXimab

- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O_2 saturation) at baseline and as clinically indicated
- No observation period is required after riTUXimab administration. Patient can be discharged from treatment room if stable whether they had a reaction or not

SUBCUTANEOUS riTUXimab

- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O_2 saturation) at baseline, at discharge and as clinically indicated
- **15 minute observation period required after each dose**

Recommended Support Medications

Drug	Dose	CCMB Administration Guideline
None required		

DISCHARGE INSTRUCTIONS/INSTRUCTIONS FOR PATIENT

- Patients should be instructed to contact their cancer team immediately if symptoms of hypersensitivity reactions occur after discharge
- There is a high risk of tumor lysis with this treatment regimen
- Instruct patient to drink 1.75 litres of water per day:
    - Two days prior to starting venetoclax
    - First day of venetoclax
    - Two days prior to and the day of each dose escalation (i.e. as part of the "ramp-up" dosing schedule)
- venetoclax tablets must be swallowed whole. Do not split, crush or chew
- Patients should notify clinic prior to starting any new medication. venetoclax has potential for significant drug-drug interactions
- Avoid grapefruit and grapefruit juice, Seville oranges (i.e. orange marmalade), and starfruit
- allopurinol must start three days prior to start of venetoclax and continues once daily until "ramp-up" is completeReinforce applicable safe handling precautions of medications, blood and body fluids during venetoclax treatment

ADDITIONAL INFORMATION

- If patient is considered at moderate to high risk for tumor lysis at the physician's discretion, the following additions may be required:
    - rasburicase (7.5 mg dose) prior to starting venetoclax
    - IV hydration
- If rasburicase is required, follow rasburicase protocol (i.e. blood specimen must be put on ice). Refer to *Diagnostic Services of Manitoba Lab Information Manual* for further information
- **Dose increases will occur at the physician's discretion and usually occur at weekly intervals during the "ramp-up". In some cases, the dose may be maintained until safe to escalate. For example, the dose may <u>not</u> be increased to next dose level if the patient is experiencing tumor lysis, tolerance issues or rapid drop in lymphocyte count**
- Patients who are on iBRUtinib may gradually taper iBRUtinib over three to five days at the physician's discretion once venetoclax treatment begins, to decrease the risk of tumor lysis
- venetoclax may only be prescribed and dispensed by physicians and pharmacists who are registered with and adhere to the guidelines of the Abbvie Distribution Program
- For the first ~5 week "ramp-up" dosing, venetoclax will be supplied to the patient at CCMB MacCharles in Winnipeg. A one-week blister pack will be supplied at a time (Venclexta® Starting Pack)
- If "ramp-up" phase needs to be prolonged, then additional 10 mg tablet pack-sizes are available
- Administration site restrictions are in place for venetoclax. For the "ramp-up", the patient must come for blood work monitoring to CCMB MacCharles site
- venetoclax will be dispensed by CCMB Pharmacy
- Administering nurse must document any infusion-related reactions with any dose of riTUXimab
- Ensure there was **no Grade 3 or 4** infusion-related reaction with any previous dose prior to administering riTUXimab via subcutaneous injection or rapid infusion
- Intravenous riTUXimab formulation is available from more than one manufacturer and uses several different brand names. Brand name will be indicated in brackets after riTUXimab. **Ensure prescription label matches the brand name on prescribed order for intravenous riTUXimab**