Regimen Reference Order – CLL– venetoclax

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

Planned Course: **Once daily until disease progression or unacceptable toxicity**
Indication for Use: **Chronic Lymphocytic Leukemia Relapsed/Refractory**

Proceed with treatment if:

Escalation ("ramp-up"):

- ***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 of less than 20 micromol/L from baseline ****
- ***LDH normal or less than 1.5 times from baseline****

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

Post Escalation (post "ramp-up"):

- ***ANC equal to or greater than 1 x 10^9/L AND Platelets equal to or greater than 30 x 10^9/L***
  - ❖ **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: • Two days prior to starting venetoclax • First dose of venetoclax • Two days prior to and the day of each 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 dose escalation is complete and patient is directed to discontinue **Alert: Contact physician if patient did not take allopurinol as directed*

Treatment Regimen – CLL– venetoclax

Drug	Dose	CCMB Administration Guideline
Dose Escalation ("ramp-up" dosing - usually 5 weeks duration)		
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 6-8 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 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 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 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*		
* 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, unless safe to escalate *Once patient's appropriate dose level is determined per prescriber assessment, one cycle = 30 day duration thereafter and continues until disease progression or unacceptable toxicity		
Days 1 to 30		
venetoclax	400 mg (4 of 100 mg tablets)	Orally once daily with food (Swallow whole) **(Self-administered at home)**
venetoclax (Venclexta ®) available dosage strengths: 10 mg, 50 mg and 100 mg tablets **Classification: Cytotoxic, Hazardous**		

REQUIRED MONITORING

Dose Escalation ("ramp-up")

Every Dose Level

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

Recommended Support Medications

Drug	Dose	CCMB Administration Guideline
Not Applicable		

INSTRUCTIONS FOR PATIENT

- 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 complete
- Patients should be instructed to contact their hematologist immediately if symptoms of hypersensitivity reactions occur after discharge
- Reinforce 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 not 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" needs to be prolonged, then additional 10mg 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