Regimen Reference Order – CLL – oBINutuzumab + venetoclax

ARIA: CLL – [oBINutuzumab + venetoclax]

Planned Course: **Cycles 1 to 6: oBINutuzumab and venetoclax (venetoclax begins on Cycle 1, Day 22) (1 cycle = 28 days)**

Cycles 7 to 12: venetoclax ONLY (1 cycle = 28 days)

Indication for Use: **Chronic Lymphocytic Leukemia**

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 increased less than 20 micromol/L above baseline****
- ***LDH is normal or less than 1.5 times baseline****

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

Cycle 1, Day 15

- ***Proceed with oBINutuzumab regardless of CBC***
  - ❖ **Contact Hematologist if parameters not met**

***Note:* Hepatitis B serology results must be reviewed in accordance with CCMB Policy Hepatitis B Monitoring for Oncology and Hematology Patients**

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 Cycle 1 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 – oBINutuzumab + venetoclax

Establish primary solution 500 mL of: normal saline

Drug	Dose	CCMB Administration Guideline
Cycle 1		
Day 1		
cetirizine	10 mg	Orally 1 hour prior to oBINutuzumab
acetaminophen	650 mg	Orally 1 hour prior to oBINutuzumab
dexamethasone	40 mg	IV in normal saline 50 mL over 15 minutes **1 hour** prior to oBINutuzumab **Nursing Alert: oBINutuzumab starts **1 hour after completion** of dexamethasone infusion*
Wait 1 hour after completion of IV pre-medication(s) before starting oBINutuzumab		
oBINutuzumab	100 mg	IV in normal saline 100 mL following administration rates below: • 0 to 60 minutes – 6 mL/hour • 60 to 120 minutes – 12 mL/hour • 120 minutes onwards – 24 mL/hour **Alert: Pharmacy to ensure final volume in bag = 100 mL (1 mg/mL final concentration)* **Nursing Alert: IV tubing is primed with oBINutuzumab*
Day 2		
cetirizine	10 mg	Orally 1 hour prior to oBINutuzumab
acetaminophen	650 mg	Orally 1 hour prior to oBINutuzumab
dexamethasone	40 mg	IV in normal saline 50 mL over 15 minutes **1 hour** prior to oBINutuzumab **Nursing Alert: oBINutuzumab starts **1 hour after completion** of dexamethasone infusion*
Wait 1 hour after completion of IV pre-medication(s) before starting oBINutuzumab		
oBINutuzumab	900 mg	IV in normal saline 250 mL following administration rates below: • 0 to 30 minutes – 14 mL/hour • 30 to 60 minutes – 28 mL/hour • 60 to 90 minutes – 42 mL/hour • 90 to 120 minutes – 56 mL/hour • 120 to 150 minutes – 69 mL/hour • 150 to 180 minutes – 83 mL/hour • 180 to 210 minutes – 97 mL/hour • 210 to 240 minutes – 111 mL/hour **Alert: Pharmacy to ensure final volume in bag = 250 mL (3.6 mg/mL final concentration)* **Nursing Alert: IV tubing is primed with oBINutuzumab*

Days 8 and 15		
cetirizine	10 mg	Orally 30 minutes prior to oBINutuzumab
acetaminophen	650 mg	Orally 30 minutes prior to oBINutuzumab
oBINutuzumab	1000 mg	**Slow Infusion:** IV in normal saline 250 mL following administration rates below: • 0 to 30 minutes – 25 mL/hour • 30 to 60 minutes – 50 mL/hour • 60 to 90 minutes – 75 mL/hour • 90 minutes onwards – 100 mL/hour **Alert:* *Pharmacy to ensure final volume in bag = 250 mL (4 mg/mL final concentration)* **Nursing Alert:* *IV tubing is primed with oBINutuzumab*
venetoclax Dose Escalation (venetoclax "ramp-up" dosing – usually 5 weeks duration)		
venetoclax Dose Level 1 (Usual duration = 7 days) – Self-administered at home		
Day 22		
venetoclax	20 mg (2 of 10 mg tablets)	Orally once with food at 6:00 a.m. (Swallow whole) **Alert:* *Post-dose biochemistry must be drawn 6 to 8 hours following Day 22 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results are available and reviewed, contact patient with results and provide dosing directions for Day 23* *Do not proceed with Day 23 venetoclax dose without confirmation of blood work*
Day 23		
venetoclax	20 mg (2 of 10 mg tablets)	Orally once with food at 6:00 a.m. (Swallow whole) **Alert:* *Post-dose biochemistry must be drawn 6 to 8 hours following Day 23 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results are available and reviewed, contact patient with results and provide dosing directions for Days 24 to 28* *Do not proceed with Day 24 venetoclax dose without confirmation of blood work*
Days 24 to 28		
venetoclax	20 mg (2 of 10 mg tablets)	Orally once daily with food at 6:00 a.m. (Swallow whole) **Alert:* *Blood work on Day 28 only required if blood work on Day 23 demonstrated evidence of biochemical tumor lysis syndrome* *If blood work required on Day 28: Biochemistry must be drawn 6 to 8 hours following Day 28 venetoclax dose. Do not proceed with Cycle 2, Day 1 venetoclax dose without confirmation of blood work*

Cycle 2		
venetoclax 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 venetoclax dose may remain at Dose Level 1 for more than a week, until safe to escalate		
Day 1 – ensure to draw blood work between 12:30 and 13:00 prior to oBINutuzumab infusion		
venetoclax	50 mg (1 of 50 mg tablet)	Orally once with food at 6:00 a.m. (Swallow whole) **(Self-administered at home)** **Alert: Post-dose biochemistry must be drawn 6 to 8 hours following Day 1 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results are available and reviewed, contact patient with results and provide dosing directions for Day 2* *Do not proceed with Day 2 venetoclax dose without confirmation of blood work*
cetirizine	10 mg	Orally 30 minutes prior to oBINutuzumab
acetaminophen	650 mg	Orally 30 minutes prior to oBINutuzumab
If applicable, wait 1 hour after completion of IV pre-medication(s) before starting oBINutuzumab		
oBINutuzumab	1000 mg	**Rapid Infusion:** IV in normal saline 250 mL following administration rates below: • 0 to 30 minutes – 25 mL/hour • 30 to 93 minutes – 225 mL/hour **Alert: Pharmacy to ensure final volume in bag = 250 mL (4 mg/mL final concentration)* **Nursing Alert: IV tubing is primed with oBINutuzumab* **OR** **Slow Infusion:** IV in normal saline 250 mL following administration rates below: • 0 to 30 minutes – 25 mL/hour • 30 to 60 minutes – 50 mL/hour • 60 to 90 minutes – 75 mL/hour • 90 minutes onwards – 100 mL/hour **Alert: Pharmacy to ensure final volume in bag = 250 mL (4 mg/mL final concentration)* **Nursing Alert: IV tubing is primed with oBINutuzumab*
Day 2		
venetoclax	50 mg (1 of 50 mg tablet)	Orally once with food at 6:00 a.m. (Swallow whole) **(Self-administered at home)** **Alert: Post-dose biochemistry must be drawn 6 to 8 hours following Day 2 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while*

		awaiting biochemistry results. Once results are available and reviewed, contact patient with results and provide dosing directions for Days 3 to 7 *Do not proceed with Day 3 venetoclax dose without confirmation of blood work*
Days 3 to 7		
venetoclax	50 mg (1 of 50 mg tablet)	Orally once daily with food at 6:00 a.m. (Swallow whole) **(Self-administered at home)** **Alert: Blood work on Day 7 only required if blood work on Day 2 demonstrated evidence of biochemical tumor lysis syndrome* *If blood work required on Day 7: Biochemistry must be drawn 6 to 8 hours following Day 7 venetoclax dose. Do not proceed with Day 8 venetoclax dose without confirmation of blood work*
venetoclax Dose Level 3* (Usual duration = 7 days) – Self-administered at home *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 venetoclax dose may remain at Dose Level 2 for more than a week, until safe to escalate		
Day 8		
venetoclax	100 mg (1 of 100 mg tablet)	Orally once with food at 6:00 a.m. (Swallow whole) **Alert: Post-dose biochemistry must be drawn 6 to 8 hours following Day 8 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results available and reviewed, contact patient with results and provide dosing directions for Day 9* *Do not proceed with Day 9 venetoclax dose without confirmation of blood work*
Day 9		
venetoclax	100 mg (1 of 100 mg tablet)	Orally once with food at 6:00 a.m. (Swallow whole) **Alert: Post-dose biochemistry must be drawn 6 to 8 hours following Day 9 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results are available and reviewed, contact patient with results and provide dosing directions Days 10 to 14* *Do not proceed with Day 10 venetoclax dose without confirmation of blood work*
Days 10 to 14		
venetoclax	100 mg (1 of 100 mg tablet)	Orally once daily with food at 6:00 a.m. (Swallow whole) **Alert: Blood work on Day 14 only required if blood work on Day 9 demonstrated evidence of biochemical tumor lysis syndrome.* *If blood work required on Day 14: Biochemistry must be drawn 6 to 8 hours following Day 14 venetoclax dose. Do not proceed with Day 15 venetoclax dose without confirmation of blood work*

venetoclax Dose Level 4* (Usual duration = 7 days) – Self-administered at home *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 venetoclax dose may remain at Dose Level 3 for more than a week, until safe to escalate		
Day 15		
venetoclax	200 mg (2 of 100 mg tablets)	Orally once with food at 6:00 a.m. (Swallow whole) **Alert: Post-dose biochemistry must be drawn 6 to 8 hours following Day 15 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results available and reviewed, contact patient with results and provide dosing directions for Day 16* *Do not proceed with Day 16 venetoclax dose without confirmation of blood work*
Day 16		
venetoclax	200 mg (2 of 100 mg tablets)	Orally once with food at 6:00 a.m. (Swallow whole) **Alert: Post-dose biochemistry must be drawn 6 to 8 hours following Day 16 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results available and reviewed, contact patient with results and provide dosing directions for Days 17 to 21* *Do not proceed with Day 17 venetoclax dose without confirmation of blood work*
Days 17 to 21		
venetoclax	200 mg (2 of 100 mg tablets)	Orally once daily with food at 6:00 a.m. (Swallow whole) **Alert: Blood work on Day 21 only required if blood work on Day 16 demonstrated evidence of biochemical tumor lysis syndrome.* *If blood work required on Day 21: Biochemistry must be drawn 6 to 8 hours following Day 21 venetoclax dose. Do not proceed with Day 22 venetoclax dose without confirmation of blood work*
venetoclax Dose Level 5* – Self-administered at home *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 venetoclax dose may remain at Dose Level 4 for more than a week, until safe to escalate		
Day 22		
venetoclax	400 mg (4 of 100 mg tablets)	Orally once with food at 6:00 a.m. (Swallow whole) **Alert: Post-dose biochemistry must be drawn 6 to 8 hours following Day 22 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results available and reviewed, contact patient with results and provide dosing directions for Day 23* *Do not proceed with Day 23 venetoclax dose without confirmation of blood work*

Day 23		
venetoclax	400 mg (4 of 100 mg tablets)	Orally once with food at 6:00 a.m. (Swallow whole) **Alert: Post-dose biochemistry must be drawn 6 to 8 hours following Day 23 venetoclax dose* *Patient does not need to stay at CancerCare Manitoba while awaiting biochemistry results. Once results available and reviewed, contact patient with results and provide dosing directions for Days 24 to 28* *Do not proceed with Day 24 venetoclax dose without confirmation of blood work*
Days 24 to 28		
venetoclax	400 mg (4 of 100 mg tablets)	Orally once daily with food at 6:00 a.m. (Swallow whole)
Cycles 3 to 6		
Day 1		
venetoclax	400 mg (4 of 100 mg tablets)	Orally once with food (Swallow whole) **(Self-administered at home)**
cetirizine	10 mg	Orally 30 minutes prior to oBINutuzumab
acetaminophen	650 mg	Orally 30 minutes prior to oBINutuzumab
If applicable, wait 1 hour after completion of IV pre-medication(s) before starting oBINutuzumab		
oBINutuzumab	1000 mg	**Rapid Infusion:** IV in normal saline 250 mL following administration rates below: • 0 to 30 minutes – 25 mL/hour • 30 to 93 minutes – 225 mL/hour **Alert: Pharmacy to ensure final volume in bag = 250 mL (4 mg/mL final concentration)* **Nursing Alert: IV tubing is primed with oBINutuzumab* **OR** **Slow Infusion:** IV in normal saline 250 mL following administration rates below: • 0 to 30 minutes – 25 mL/hour • 30 to 60 minutes – 50 mL/hour • 60 to 90 minutes – 75 mL/hour • 90 minutes onwards – 100 mL/hour **Alert: Pharmacy to ensure final volume in bag = 250 mL (4 mg/mL final concentration)* **Nursing Alert: IV tubing is primed with oBINutuzumab*
Days 2 to 28		
venetoclax	400 mg (4 of 100 mg tablets)	Orally once daily with food (Swallow whole) **(Self-administered at home)**

Cycles 7 to 12		
Days 1 to 28		
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: Non-cytotoxic, Hazardous**		

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

REQUIRED MONITORING

Hepatitis B serology

- Hepatitis B surface antigen and Hepatitis B core antibody (drawn within preceding 5 years)

Cycle 1

Day 1

- CBC, serum creatinine, urea, sodium, potassium, phosphate, calcium, liver enzymes, LDH, total bilirubin, total protein, glucose, albumin and uric acid as per Physician Orders
- Baseline HIV serology
- Baseline EKG at physician's discretion

Day 8

- No blood work required

Day 15

- CBC, serum creatinine, urea, sodium, potassium, phosphate, calcium, liver enzymes, LDH, total bilirubin, total protein, glucose, albumin and uric acid as per Physician Orders

Day 16 or 17

- Hematologist assessment to determine tumor lysis risk and venetoclax dosing

Days 22 and 23

- CBC, serum creatinine, urea, potassium, phosphate, calcium, liver enzymes, LDH, albumin and uric acid as per Physician Orders
    - At baseline prior to venetoclax initial dose (on Day 21), then
    - 6 to 8 hours post venetoclax on Day 22, then
    - 6 to 8 hours post venetoclax on Day 23, then
    - As per Physician Orders, to determine ongoing dose of venetoclax

Day 28 (**only** if cycle 1, day 23 blood work demonstrated evidence of biochemical tumor lysis syndrome)

- CBC, serum creatinine, urea, sodium, potassium, phosphate, calcium, liver enzymes, LDH, total bilirubin, total protein, glucose, albumin and uric acid as per Physician Orders
    - 6 to 8 hours post venetoclax on Day 28

Cycle 2

Days 1, 2, 8, 9, 15, 16, 22 and 23

- CBC, serum creatinine, urea, potassium, phosphate, calcium, liver enzymes, LDH, albumin and uric acid as per Physician Orders
    - 6 to 8 hours post venetoclax on Days 7, 14 and 21, then
    - 6 to 8 hours post venetoclax on Days 1, 8, 15 and 22, then
    - 6 to 8 hours post venetoclax on Days 2, 9, 16 and 23, then
    - As per Physician Orders, to determine ongoing dose of venetoclax

Day 7 (**only** if day 2 blood work demonstrated evidence of biochemical tumor lysis syndrome)

- CBC, serum creatinine, urea, sodium, potassium, phosphate, calcium, liver enzymes, LDH, total bilirubin, total protein, glucose, albumin and uric acid as per Physician Orders
    - 6 to 8 hours post venetoclax on Day 7

Day 14 (**only** if day 9 blood work demonstrated evidence of biochemical tumor lysis syndrome)

- CBC, serum creatinine, urea, sodium, potassium, phosphate, calcium, liver enzymes, LDH, total bilirubin, total protein, glucose, albumin and uric acid as per Physician Orders
    - 6 to 8 hours post venetoclax on Day 14

Day 21 (**only** if day 16 blood work demonstrated evidence of biochemical tumor lysis syndrome)

- CBC, serum creatinine, urea, sodium, potassium, phosphate, calcium, liver enzymes, LDH, total bilirubin, total protein, glucose, albumin and uric acid as per Physician Orders
    - 6 to 8 hours post venetoclax on Day 21

Days 23 and 24

- Hematologist assessment to determine tumor lysis risk and venetoclax dosing

Cycles 3 to 12

Day 1

- CBC, serum creatinine, urea, sodium, potassium, phosphate, calcium, liver enzymes, LDH, total bilirubin, total protein, glucose, albumin and uric acid as per Physician Orders

oBINutuzumab monitoring

- 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 oBINutuzumab administration. Patient can be discharged from treatment room if stable whether they had a reaction or not

Recommended Support Medications

Drug	Dose	CCMB Administration Guideline
None required		

DISCHARGE INSTRUCTIONS

- Patients should be instructed to contact their cancer team immediately if symptoms of hypersensitivity reactions occur after discharge
- There is a 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 (until 24 hours after first dose of venetoclax)
    - Two days prior to and the day of each dose escalation (until 24 hours after each venetoclax dose escalation) (i.e. as part of the "ramp-up" dosing schedule)
- venetoclax tablets should be swallowed whole. Do not split, crush or chew
- venetoclax has potential for significant drug-drug interactions. Patients should notify clinic prior to starting any new medication
- Avoid grapefruit and grapefruit juice, Seville oranges (i.e. orange marmalade) and starfruit
- allopurinol must start three days prior to start of Cycle 1 and continues once daily until "ramp-up" is complete and patient is directed to discontinue

ADDITIONAL INFORMATION

- Due to the risk of reactivation of Hepatitis B virus (HBV) while on this treatment regimen, prescriber must adhere to CCMB Policy ***Hepatitis B Monitoring for Oncology and Hematology Patients*** for ordering and interpreting HBV serology and prescribing antiviral prophylaxis
- 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) 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
- venetoclax ramp-up to be prescribed by hematologist
- **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**
- Administering nurse must document any infusion-related reactions with any dose of oBINutuzumab
- Ensure there were **no Grade 3 or 4** infusion-related reactions with the three preceding infusions prior to administering oBINutuzumab via rapid infusion. Patients will be switched to rapid infusion at Cycle 2, Day 1 if lymphocyte count is less than 5×10^9/L
- **Note: For Cycles 2 to 6**, an entry called ***"Physician Reminder – oBINutuzumab infusion time 1 Units Insert Miscellaneous once"*** will appear in the electronic drug order. No action is required. **This prompt is to remind the prescriber to confirm that patient is eligible for oBINutuzumab rapid infusion**
- For Cycle 1, Days 1 and 2, oBINutuzumab administration is 6 to 8 hours on average. Treatment should be booked for earliest morning appointment
- 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
- venetoclax will be dispensed by CCMB Pharmacy