Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

Obinutuzumab-Venetoclax (Low Risk)

Regimen

- CLL – Obinutuzumab-Venetoclax (Low Risk)

Indication

- Chronic lymphatic leukaemia (CLL) or small lymphocytic lymphoma (SLL) in adult patients where;

  - there is 17p deletion or TP53 mutation
  - there is no 17p deletion or TP53 mutation and for whom cyclophosphamide, fludarabine, and rituximab or bendamustine and rituximab are unsuitable
  - there is no 17p deletion or TP53 mutation for whom cyclophosphamide, fludarabine, and rituximab or bendamustine and rituximab are suitable

  and all the criteria as described in the appropriate Bluteq form are met and an application for use has been approved.

Toxicity

Drug	Adverse Effect
Obinutuzumab	Infusion related reactions, progressive multifocal leukoencephalopathy (PML), cardiac toxicity, thrombocytopenia, neutropenia, tumour lysis syndrome
Venetoclax	Upper respiratory tract infection, neutropenia, anaemia, hyperphosphataemia, electrolyte disturbances, tumour lysis syndrome (TLS), gastrointestinal disturbance, raised blood creatinine, fatigue.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring (Treatment only)

- Hepatitis B status prior to starting treatment. Patients with positive hepatitis B serology should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent hepatitis re-activation. Viral screening is also required before starting treatment for hepatitis C and HIV status.

- Tumour burden assessment, including radiographic evaluation (e.g., CT scan) must be performed for all patients prior to starting therapy.

- Assess risk for tumour lysis syndrome (TLS) including uric acid and bone profile prior to cycle one in those considered at risk of tumour lysis syndrome (please refer to table one for description of high, low and moderate risk TLS).

- When starting venetoclax FBC, U&Es and LFTs (to include phosphate, calcium and LDH) on cycle one days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30 of venetoclax

administration (not cycle days)

- These parameters must be checked prior to any venetoclax dose increase. Consider on day 1 of subsequent cycles or refer to local guidelines.

- FBC, U&Es (including potassium, phosphate, LDH, adjusted calcium and uric acid) and LFTs should be measured prior to starting therapy and pre-existing electrolyte abnormalities corrected. For patients at risk of tumour lysis syndrome (TLS), potassium, uric acid, phosphate, adjusted calcium, LDH and creatinine should be monitored at 6 to 8 hours and at 24 hours after the first dose and during each dose increase 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 (see section on TLS below). Consider admitting the patient for monitoring for TLS monitoring and treatment. During the ramp-up phase, the FBC counts needs to be considered prior to next dose escalation, while FBC counts at 6 to 8 hours and at 24 hours after the first dose and during each dose increase of venetoclax are not to be considered for TLS risk or dose modification.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if the patient is symptomatic of anaemia or where the haemoglobin is less than 8g/dL.

At the start of each cycle the neutrophil count should be equal to or greater that $1x10^9$/L and the platelets equal to or greater than $100x10^9$/L.

Haematological Toxicity	Obinutuzumab	Venetoclax
Grade 3 or 4 haematological toxicity, febrile neutropenia or thrombocytopenic bleeding that delays treatment by less than 4 weeks	Hold until the above parameters are met then restart at usual dose.	Withhold for NCI-CTC grade 3 or 4 febrile neutropenia and/or infection, or other grade 4 haematological toxicities, except lymphopenia. Once the toxicity has resolved to NCI-CTC grade 1 or baseline level (recovery), therapy may be restarted at the same dose.

		If the toxicity recurs, the dose reduction guidelines in table 2 should be followed when resuming treatment following recovery. A larger dose reduction may occur at the discretion of the responsible consultant. Discontinuation of venetoclax should be considered in patients who require dose reductions to less than 100 mg for more than 2 weeks
Grade 3 or 4 haematological toxicity that delays treatment by more than 4 weeks	Discontinue	

Hepatic Impairment

Patients with hepatic impairment should be closely monitored for signs and symptoms of toxicity.

The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established.

No dose adjustments are required in patients with mild or moderate hepatic impairment. These patients should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase as a trend for increased adverse events was observed in patients with moderate hepatic impairment in a population pharmacokinetic analysis.

It is not recommended to administer venetoclax to patients with severe hepatic impairment as safety in this patient group has not been established.

Renal Impairment

Patients with evidence of impaired renal function should be carefully monitored as they are prone to additional myelosuppression.

Dose adjustment is not considered necessary for obinutuzumab in those with mild to moderate renal impairment.

For venetoclax no dose adjustment is required for patients with mild or moderate renal impairment. However, patients with reduced renal function (CrCl less than 80 ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of tumour lysis syndrome at initiation and during the dose-titration phase.

Safety in patients with severe renal impairment or on dialysis has not been established for venetoclax, and 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.

Toxicity	Obinutuzumab dose
Grade 2 or 3 related organ/non- haematological toxicity	Hold until less than or equal to grade 1
Grade 2 non haematological toxicity that delays treatment by more than 4 weeks	Discontinue
Grade 4 related organ/non- haematological toxicity, severe haemorrhage, severe skin reaction, pneumonitis, severe arrhythmias or other severe cardiovascular events	Discontinue
Viral hepatitis or other serious infections; reactivation of hepatitis B	Discontinue

Other

Toxicity	Obinutuzumab dose
Grade 2 or 3 related organ/non- haematological toxicity	Hold until less than or equal to grade 1
Grade 2 non haematological toxicity that delays treatment by more than 4 weeks	Discontinue
Grade 4 related organ/non- haematological toxicity, severe haemorrhage, severe skin reaction, pneumonitis, severe arrhythmias or other severe cardiovascular events	Discontinue
Viral hepatitis or other serious infections; reactivation of hepatitis B	Discontinue

Obinutuzumab

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre- existing neurologic manifestations. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Infusion Reactions

Obinutuzumab administration is associated with infusion related reactions, particularly during the first cycle.

Most frequently reported symptoms associated with an infusion related reaction were nausea, chills, hypotension, pyrexia, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia, and diarrhoea. Respiratory and cardiac symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and atrial fibrillation have also been reported.

Anaphylaxis has been reported during administration of obinutuzumab. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion must be stopped and treatment permanently discontinued.

Appropriate pre-medication must be administered before each infusion to reduce the risk of infusion related reactions.

Infusion related reactions should be treated as described in the table below.

Toxicity Grade	Obinutuzumab
1-2	Reduce the infusion rate by half and treat symptoms. Restart the infusion once symptoms have resolved. Escalate infusion rate as tolerated at increments appropriate for treatment
1episode of grade 3	Hold infusion and treat the symptoms. Restart the infusion once the symptoms have resolved at no more than half the previous rate. Escalate the infusion rate as tolerated at increments appropriate for the treatment dose (see below) The day 1 (cycle 1) infusion rate may be increased back up to 25mg/hr after 60 minutes, but not increased further
2nd episode of grade 3 (during same or subsequent infusion)	Infusion must be stopped and therapy must be permanently discontinued
Grade 4 or acute life threatening respiratory reactions	Infusion must be stopped and therapy must be permanently discontinued

Tumour Lysis Syndrome (TLS)

Tumour lysis syndrome (TLS) has been reported with obinutuzumab and in patients during the titration phase of venetoclax. Patients who are considered to be at risk of TLS (e.g. patients with a high tumour burden and/or a high circulating lymphocyte count (greater than $25x10^9$/L) and/or renal impairment (CrCl less than 70 ml/min) should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of allopurinol or a suitable alternative such as rasburicase 7.5mg starting 12-24 hours prior to the infusion. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed. For example, the BTS guidelines. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Table 1 - **Tumour Lysis Syndrome (TLS) Management Venetoclax**

Abnormality	Dose Modification and Management
Hyperkalaemia	
Potassium more than ULN	• Hold venetoclax until resolution • Do an ECG and apply local trust hyperkalaemia policy • Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour. If the potassium is less than ULN continue to monitor for TLS 2 and 4 hours later • If the potassium is more than or equal to 6.0mmol/l and/or symptomatic (e.g. muscle cramps, weakness, paraesthesia, nausea, vomiting or diarrhoea) then seek advice from a specialist renal team.
Hyperuricaemia	
Uric acid more than than ULN	• Hold venetoclax until resolution. • Consider giving rasburicase if not given in last 24 hours.
Hypocalcaemia	
Adjusted calcium less than LLN or patient symptomatic (e.g. muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcaemia.	• Hold the venetoclax until resolution. • Administer calcium gluconate 10% 10 to 20ml in 100ml sodium chloride 0.9% over 15minutes with ECG monitoring. • Recheck calcium, creatinine, phosphate, potassium and uric acid every one to two hours.
Hyperphosphataemia	
Phosphate more than ULN	• Withold the venetoclax until resolution to less than 1.45mmol/l • Discuss with the local renal team as a phosphate binder may be necessary (e.g. calcium carbonate, sevelamer, lanthanum) • Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour.
Creatinine	
Creatinine more than ULN Increase of more than or equal to 25% from baseline.	• Hold the venetoclax until resolution • Administer intravenous fluids. • Recheck potassium, phosphate, uric acid, calcium and creatinine in 1 to 2 hours

Regimen

28 day cycle for 6 cycles for treatment and 6 cycles for maintenance (12 cycles in total)

Cycle 1

Drug	Dose	Days	Administration
Obinutuzumab	100mg	1	Intravenous infusion in 100ml sodium chloride 0.9% at a rate of 25mg/hour (over 240 minutes)*
Obinutuzumab	900mg	2	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 50mg/hour*
Obinutuzumab	1000mg	8, 15	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*
Venetoclax	20mg	22, 23, 24, 25, 26, 27, 28	Oral

Cycle 2

Drug	Dose	Days	Administration
Obinutuzumab	1000mg	1	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*
Venetoclax	50mg	1, 2, 3, 4, 5, 6, 7	Oral
Venetoclax	100mg	8, 9, 10, 11, 12, 13, 14	Oral
Venetoclax	200mg	15, 16, 17, 18, 19, 20, 21	Oral
Venetoclax	400mg	22, 23, 24, 25, 26, 27, 28	Oral

Cycle 3, 4, 5, 6

Drug	Dose	Days	Administration
Obinutuzumab	1000mg	1	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*
Venetoclax	400mg	1-28 inclusive	Oral

Cycles 7, 8, 9, 10, 11, 12

Drug	Dose	Days	Administration
Venetoclax	400mg	1-28 inclusive	Oral

*Please see administration information below for infusion rates

Dose Information

- Venetoclax is available as 10mg, 50mg and 100mg film-coated tablets.

- 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 400mg, tumour lysis syndrome risk should be reassessed to determine if restarting at a reduced dose is necessary.

Administration Information

- Withhold antihypertensive treatments 12 hours before, during and 1 hour after the obinutuzumab infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their antihypertensive medicines

- Obinutuzumab standard infusion rates, in the absence of reactions are as follows;

Cycle	Day of Treatment	Rate of Infusion
1	Day 1 (100mg in 100ml)	Administer at 25mg/hour (over 240 minutes). Do not increase the rate
1	Day 2 (or day 1 continued) (900mg in 250ml)	Start the administration at 50mg/hour The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400mg/hour
1	Day 8, 15 (1000mg in 250ml)	Infusions can be started at a rate of 100mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400mg/hour
2 onwards	All days (1000mg in 250ml)	Infusions can be started at a rate of 100mg/hour and increased by 100mg/hour increments every 30 minutes to a maximum of 400mg/hour

- The recommended dose of obinutuzumab is 1000 mg administered over day 1 and day 2, and on day 8 and day 15 of the first treatment cycle. Two infusion bags should be prepared for the infusion on days 1 and 2 (100 mg for day 1 and 900 mg for day 2).

- If the first infusion (100mg) is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg the second infusion (900mg) must be administered the following day.

- Venetoclax film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole with a meal and water at approximately the same time each day. The 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.

- It is imperative that the time of administration of the venetoclax is recorded on ARIA and the correct blood tests are taken at the correct time as part of any increase in the dose.

- 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.

Additional Treatment

- Antiemetics 15-30 minutes

  - metoclopramide 10mg three times a day when required (supplied on cycle 1 and 2 only)

- Premedication for obinutuzumab infusion reactions

  - sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

  then as follows;

Pre-medication (60 minutes prior to obinutuzumab)	**Cycle 1 days 1 and 2**	**Cycle 1 days 8 and 15 and Cycles 2, 3, 4, 5, 6**		
	All Patients	**Patients without infusion related reactions**	**Patients with grades 1-2 infusion related reactions**	**Patients with a grade 3 infusion related reactions or with a lymphocyte count greater than $25x10^9$/L**
Methylprednisolone sodium succinate 80mg intravenous	√			√
Chlorphenamine 10mg intravenous	√		√	√
Paracetamol 1000mg oral	√	√	√	√

On an as required basis;

- chlorphenamine 10mg intravenous for infusion reactions
- lorazepam 1mg oral for rigors
- methylprednisolone sodium succinate 80mg intravenous for infusion reactions
- paracetamol 1000mg oral for pyrexia

- pethidine 25mg intravenous in 10ml sodium chloride 0.9% over 5 minutes for rigors following a verbal confirmation to administer from a doctor.

- Allopurinol 300mg oral starting two days prior to day one cycle one for 7 days in total (not included in ARIA). Rasburicase 7.5mg intravenous infusion may be required for high risk individuals.

- Anti-infective prophylaxis as follows;

- consider aciclovir 400mg twice a day oral (consultants discretion, included on ARIA)
- consider co-trimoxazole 960 mg once daily on Mon, Wed, Fri (consultants discretion, included on ARIA)

Mouthwashes as per local formulary. For example;
- nystatin 4ml four times daily (consultants discretion, not included on ARIA)
- chlorhexidine 10ml four times daily (consultants discretion, not included on ARIA)

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to venetoclax.

- It must be made clear to all staff, including those in the community, that venetoclax should only be prescribed under the supervision of a consultant haematologist.

- Venetoclax interacts with many other medications. Always check for drug interactions.

- Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax.

- Hypotension may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine

References

1. Dawson K, Moran M, Guindon K et al. Managing infusion related reactions for patients with chronic lymphocytic leukemia receiving obinutuzumab. Clin J Oncol Nursing 2016; 20 (2): 41-48
2. National Institute for Health and Care Excellence. Technology Appraisal Guidance 663 (2020). Venetoclax and obinutuzumab for untreated chronic lymphocytic leukemia. DOH:London

REGIMEN SUMMARY

Obinutuzumab-Venetoclax (Low Risk)

Cycle 1

Day 1

1. Warning – TLS Assessment and Prevention
   Administration Instructions
   There is a risk of tumour lysis syndrome in CLL patients having this regimen. Ensure the patient has been assessed for TLS risk and prescribe the appropriate prophylaxis. This regimen is for low risk individuals. Allopurinol may be required prior to the obinutuzimab; it is not included in this protocol. It is included prior to the venetoclax dose escalations. Ensure arrangements are in place to monitor the patient appropriately.

2. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

3. Chlorphenamine 10mg intravenous
   Administration Instructions
   Administer 60 minutes prior to obinutuzumab

4. Methylprednisolone sodium succinate 80mg intravenous
   Administration Instructions
   Administer 60 minutes prior to obinutuzumab

5. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient takes regular paracetamol for pain control and take dose into account
   Administer 60 minutes prior to obinutuzumab

6. Obinutuzumab 100mg intravenous infusion in 100ml sodium chloride 0.9% over 240 minutes
   Administration Instructions
   Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

7. Chlorphenamine 10mg when required for infusion related reactions
   Administration Instructions
   For the relief of infusion related reactions

8. Lorazepam 1mg oral when required for rigors
   Administration Instructions
   For the relief of rigors

9. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
   Administration Instructions
   For the relief of infusion related reactions

10. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

11. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Day 2

12. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

13. Chlorphenamine 10mg intravenous
    Administration Instructions
    Administer 60 minutes prior to obinutuzumab

14. Methylprednisolone sodium succinate 80mg intravenous
    Administration Instructions
    Administer 60 minutes prior to obinutuzumab

15. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account
    Administer 60 minutes prior to obinutuzumab

16. Obinutuzumab 900mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions
    Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

17. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

18. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

19. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

20. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

21. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Day 8

22. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

23. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than $25x10^9$/L

24. Methylprednisolone sodium succinate 80mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reaction

25. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

26. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions
    Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

27. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

28. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

29. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

30. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

31. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Day 15

32. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

33. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than $25x10^9$/L

34. Methylprednisolone sodium succinate 80mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reaction

35. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

36. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride over 240 minutes
    Administration Instructions
    Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

37. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions

For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

38. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

39. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

40. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

41. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Take Home Medicines (day 1 only)

42. Allopurinol 300mg once a day oral starting 72 hours before the first dose of venetoclax
    Administration Instructions
    Start 72 hours prior to the administration of the first dose of venetoclax and stop after 7 days of the 400mg dose escalation. Please supply 38 days or nearest equivalent original pack size.

43. Metoclopramide 10mg three times a day when required for the relief of nausea
    Administration Instructions
    Please supply 28 tablets or nearest original pack size

44. Aciclovir 400mg twice a day oral for 28 days

45. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days

46. Warning Consider Mouthwashes
    Administration Instructions
    Consider prescribing mouthwash (from favourites) such as
    - nystatin 4ml four times a day
    - chlorhexidine 10ml four times a day

Take Home Medicines (Day 22 only)

47. Warning – TLS prevention
    Administration Instructions
    There is a risk of tumour lysis syndrome in CLL patients having this regimen. Ensure the patient has been assessed for TLS risk and prescribe the appropriate prophylaxis. This regimen is for low risk individuals. Please check the patient has taken the prescribed allopurinol.

    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 2L 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.

    Ensure arrangements are in place to monitor the patient appropriately.

48. Venetoclax 20mg once a day for 7 days oral
Administration Instructions
Take with or just after food. Take with a full glass of water.

Oral SACT

Cycle 2

49. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

50. Chlorphenamine 10mg intravenous when required for infusion related reactions
Administration Instructions
Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than $25x10^9$/L

51. Methylprednisolone sodium succinate 80mg intravenous when required for infusion related reactions
Administration Instructions
Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reactions

52. Paracetamol 1000mg oral
Administration Instructions
Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

53. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
Administration Instructions
Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

54. Chlorphenamine 10mg when required for infusion related reactions
Administration Instructions
For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

55. Lorazepam 1mg oral when required for rigors
Administration Instructions
For the relief of rigors

56. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
Administration Instructions
For the relief of infusion related reactions

57. Paracetamol 1000mg oral when required for pyrexia
Administration Instructions
For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

58. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
Administration Instructions
For the relief of rigors following a verbal confirmation to administer from a doctor

Take Home Medicines

Day 1

59. Venetoclax 50mg once a day for 7 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

60. Aciclovir 400mg twice a day oral for 28 days

61. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days

Day 8

62. Venetoclax 100mg once a day for 7 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

Day 15

63. Venetoclax 200mg once a day for 7 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

Day 22

64. Venetoclax 400mg once a day for 7 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

Cycles 3, 4, 5, 6

65. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

66. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than than $25x10^9/L$

67. Methylprednisolone sodium succinate 80mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reaction

68. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

69. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions

Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

70. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

71. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

72. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

73. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

74. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Take Home Medicines

Day 1

75. Venetoclax 400mg once a day for 28 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

76. Aciclovir 200mg twice a day oral for 28 days

77. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 day

Cycles 7, 8, 9, 10, 11, 12

79. Venetoclax 400mg once a day for 28 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

80. Aciclovir 400mg twice a day oral for 28 days

81. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	May 2021	None	Dr Deborah Wright Pharmacist	Prof F Forconi Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols are only one source of information. They should be read in conjunction with the latest Summary of Product Characteristics and published information.