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| CLL Indication | For the treatment of untreated chronic lymphatic leukaemia (CLL) or small lymphocytic lymphoma (SLL) either: <ul style="list-style-type: none"> in the presence of 17p deletion and/or <i>TP53</i> mutation, in the absence of 17p deletion and <i>TP53</i> mutation suitable or unsuitable for either FCR (fludarabine, cyclophosphamide and rituximab) or BR (bendamustine and rituximab) treatment. |
| Treatment Intent | Disease Modification. |
| Frequency and number of cycles | Repeat every 28 days Obinutuzumab: maximum of 6 cycles Venetoclax: 5 weeks titration of venetoclax starting on day 22 of cycle 1 and completing on day 28 of cycle 2. Continue venetoclax until disease progression or unacceptable toxicity or patient choice to stop treatment or for the maximum treatment duration of 12 cycles. Formal medical review as to whether treatment should continue should be scheduled to take place by the end of the first 8 weeks of treatment. |
| Monitoring Parameters pre-treatment | <ul style="list-style-type: none"> Check virology status prior to start of treatment. Bloods cycle 1: Monitor FBC, U&Es and LFTs Day 1, Day 8, Day 15 and Day 22. From day 22 of cycle 1, monitor FBC every day or on alternate days until the end of cycle 1. For patients at risk of tumour lysis syndrome (TLS), blood chemistries should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax. Bloods cycle 2: Monitor FBC, U&Es and LFTs weekly. Bloods cycle 3 onwards: Monitor FBC, U&Es and LFTs prior to each cycle or as clinically indicated. Neuts must be ≥ 0.5 and PLT must be ≥ 25. U&Es (potassium, uric acid, phosphorous, calcium and creatinine) should be assessed prior to the initial dose to evaluate kidney function and correct pre-existing abnormalities. Haematological toxicity: If neutrophils $< 1.0 \times 10^9/L$ and / or platelets $< 80 \times 10^9/L$, delay until counts have recovered, then continue with full dose obinutuzumab. After first neutropenic event, subsequent cycles should be given prophylactic GCSF. Patients who experience neutropenia should be closely monitored; it is recommended that patients with severe neutropenia lasting more than 1 week receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Late onset neutropenia (occurring > 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) may occur. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. <u>Tumour Lysis Syndrome (TLS)</u> Changes in electrolytes consistent with TLS can occur as early as 6 to 8 hours following the first dose and at each dose increase. Patients with a high tumour burden ($> 25 \times 10^9/L$) and reduced renal function (CrCl < 80 mL/min) are at greatest risk of TLS. All patients should have white cell count less than $25 \times 10^9/L$ prior to initiation of venetoclax. Cytoreduction prior to treatment may be required. For patients at risk of tumour lysis syndrome (TLS), electrolyte abnormalities should be corrected promptly. The next venetoclax dose should not be administered until the 24 hour blood chemistry results have been evaluated. |

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| | <ul style="list-style-type: none"> • Blood chemistries should be monitored pre-dose, and at 6 to 8 hours and at 24 hours after each new dose. The same monitoring schedule should be followed for patients who continue to be at risk. Blood chemistries should be reassessed prior to each cycle. • Anti-hyperuricaemic agents should be administered prior to starting treatment and be continued for the first 3 cycles and beyond as clinically appropriate. Rasburicase, if required, should be initiated by a consultant. Review and amend as necessary allopurinol prescription. • All patients should be adequately hydrated during the dose titration phase of venetoclax to reduce the risk of TLS. Patients should be particularly instructed to drink 1.5 - 2 litres 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. • For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pre-treatment lactate dehydrogenase (LDH) levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose. • Hepatic impairment <ul style="list-style-type: none"> ○ Obinutuzumab has not been studied in patients with impaired hepatic function, no recommendation available. ○ Venetoclax: No dose adjustment for mild to moderate but close monitoring required in moderate impairment for signs of toxicity at initiation and during titration. A dose reduction of at least 50% is recommended in severe impairment. • Renal impairment: <ul style="list-style-type: none"> ○ Obinutuzumab: no dose adjustment is required if CrCl \geq 30ml/min; there is no data for CrCl < 30ml/min. ○ Venetoclax: No dose adjustment for mild to moderate (CrCl \geq 30ml/min and < 90ml/min). Patients with reduced renal function (CrCl < 80ml/min) may require extra support and monitoring for TLS during induction and titration phase. Patients with severe renal impairment (CrCl < 30ml/min) should only be administered venetoclax if the benefits outweigh the risks and they should be monitored more closely for signs of toxicity and TLS. • Infusion-related reactions: <ul style="list-style-type: none"> • Patients with a history of cardiac disease should be monitored closely. • Due to the risk of hypotension during infusion withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each infusion and for the first hour after administration. • In the event of an infusion related reaction (IRR), the administration rate should be modified as follows: <ul style="list-style-type: none"> • Grade 1-2 IRR (mild-moderate): Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. • Grade 3 IRR (severe): Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If a grade 3 IRR occurs at re-challenge, stop infusion immediately and discontinue therapy permanently. • Grade 4 IRR (life threatening): Stop infusion and discontinue therapy. |
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| | <ul style="list-style-type: none"> • Management of adverse reactions and dose adjustments: <ul style="list-style-type: none"> ○ Obinutuzumab: no recommend dose adjustments. ○ Venetoclax: If a 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 above). Treatment with Venetoclax should be withheld for any grade 3 or 4 non-haematological toxicities, grade 3 or 4 neutropenia with infection or fever, or grade 4 haematological toxicities, except lymphopenia. Once the 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 following resolution. A larger dose reduction may be made at clinician discretion. For patients who require dose reductions to less than 100 mg for more than 2 weeks, discontinuation of venetoclax should be considered. ○ 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 after completing the dose-titration phase, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g. all or some levels of the dose titration; see Table 1). ○ Progressive multifocal leukoencephalopathy (PML): PML has been reported in patients receiving obinutuzumab. Patients should be monitored for new or worsening neurological, cognitive or behavioural changes. All treatment should be held if PML is suspected and permanently discontinued if PML is confirmed. • Common drug interactions(for comprehensive list refer to BNF/SPC): <ul style="list-style-type: none"> ○ Venetoclax: Concomitant use with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities. Concomitant use with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole) at initiation and during the dose-titration phase is contraindicated. Concomitant use with moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) 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 and titration doses of venetoclax should be reduced by at least 50%. Patients should be monitored more closely for signs of toxicities. For patients who are on a steady daily dose, the venetoclax should be reduced by 50% when used concomitantly with moderate CYP3A inhibitors and 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 strong (e.g., carbamazepine, phenytoin, rifampin) or moderate (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) CYP3A4 inducers should be avoided. Concomitant use of preparations containing St John's Wort is contraindicated. Co-administration of bile acid sequestrants with venetoclax is not recommended. It is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin. Inhibitors of P-gp or BCRP may increase venetoclax exposure; these should be avoided at initiation of treatment and during the titration phase. Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, |
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| | <p>dabigatran, everolimus, sirolimus) with venetoclax should be avoided.</p> <ul style="list-style-type: none"> ○ If statins are given concomitantly with venetoclax monitor for statin toxicity. ○ Avoid grapefruit products, Seville oranges and starfruit. ○ Obinutuzumab: No formal drug-drug interaction studies have been performed. <ul style="list-style-type: none"> ● Missed dose: ● If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned 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. ● 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. ● Live vaccines should not be administered during treatment and thereafter until B-cell recovery. ● NB Complete Obinutuzumab monitoring/administration details. |
| References | KMCC protocol HAEM-CLL-034 v1 KMCC protocol HAEM-NHL-083 SPC accessed online 11.11.20 Blueteq forms accessed online 11.11.20 |

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Dose modification of venetoclax for TLS and other toxicities

| Dose at interruption (mg) | Restart dose (mg ^a) |
|---------------------------|---------------------------------|
| 400 | 300 |
| 300 | 200 |
| 200 | 100 |
| 100 | 50 |
| 50 | 20 |
| 20 | 10 |

^aThe modified dose should be continued for 1 week before increasing the dose.

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Cycle 1: 28 day cycle

| Day | Drug | Dose | Route | Infusion Duration | Administration | |
|---|---|--------------|-----------|---|--|--|
| Day 1 | Methylprednisolone | 80mg | IV | Over 15 min | In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion. | |
| | Paracetamol | 1g | PO | STAT | Given at least 30 minutes before the obinutuzumab infusion. | |
| | Chlorphenamine | 10mg | IV | Slow bolus over 1min | | |
| | Ensure adequate IV hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10 ⁹ /L to reduce the risk of TLS. | | | | | |
| | OBINUTUZUMAB | 100mg | IVI | See below | In 100ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9% | |
| <ul style="list-style-type: none"> <u>Obinutuzumab infusion rate notes:</u> Administer at 50 mg/hr. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 50 mg per hour every 30 minutes to a maximum rate of 400 mg per hour. | | | | | | |
| Day 2 | Methylprednisolone | 80mg | IV | Over 15 min | In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion. | |
| | Paracetamol | 1g | PO | STAT | Given at least 30 minutes before the obinutuzumab infusion. | |
| | Chlorphenamine | 10mg | IV | Slow bolus over 1 min | | |
| | Ensure adequate IV hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10 ⁹ /L to reduce the risk of TLS. | | | | | |
| | OBINUTUZUMAB | 900mg | IV | See above | In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9% | |
| Day 8 | Methylprednisolone | 80mg | IV | Over 15 min | In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion. | |
| | Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10 ⁹ /L | | | | | |
| | Paracetamol | 1g | PO | STAT | Given at least 30 minutes before the obinutuzumab infusion. | |
| | Chlorphenamine | 10mg | IV | Slow bolus over 1 min | | |
| | Omit if patient tolerated previous obinutuzumab infusion. | | | | | |
| Ensure adequate IV hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10 ⁹ /L to reduce the risk of TLS. | | | | | | |
| OBINUTUZUMAB | 1000mg | IVI | See above | In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9% | | |

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| Day 15 | Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10 ⁹ /L | 80mg | IV | Over 15 min | In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion. | |
| | Paracetamol | 1g | PO | STAT | Given at least 30 minutes before the obinutuzumab infusion. | |
| | Chlorphenamine Omit if patient tolerated previous obinutuzumab infusion. | 10mg | IV | Slow bolus over 1min | | |
| | Ensure adequate IV hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10 ⁹ /L to reduce the risk of TLS. | | | | | |
| | OBINUTUZUMAB | 1000mg | | IVI | See above | In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9% |
| Day 22 | Venetoclax titration | See TTO | PO | | | |
| TTO | Drug | Dose | Route | Directions | | |
| Start titration on day 22 of cycle 1 | VENETOCLAX (available as 10mg, 50mg and 100mg tablets) | See administration details For escalation schedule. | | PO | Start on day 22 of cycle 1 and continue titration through cycle 2. Take 20mg OD for 1 week. Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing. During dose titration the dose should be taken in the morning. | |
| | Metoclopramide | 10mg | | PO | Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously. | |
| | Allopurinol | 300mg | | PO | OD, Start 24 hours before treatment. For the first 3 cycles based on clinical judgement of tumour burden eg WBC count, extent of lymphadenopathy Review if alternative anti-hyperuricaemic agent required. If Rasburicase is needed, then hold Allopurinol. Restart allopurinol after uric acid levels have settled and Rasburicase has been stopped. | |
| | Aciclovir | 400mg | | PO | BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose) | |
| | Co-trimoxazole | 480mg | | PO | TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose) | |
| | Consider prophylactic anti-fungal | | | | | |

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Cycle 2: 28 day cycle

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|-------|---|--|
| Day 1 | Methylprednisolone | 80mg | IV | Over 15 min | In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion. |
| | Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10 ⁹ /L | | | | |
| | Paracetamol | 1g | PO | STAT | Given at least 30 minutes before the obinutuzumab infusion. |
| | Chlorphenamine | 10mg | IV | Slow bolus over 1 min | |
| Omit if patient tolerated previous obinutuzumab infusion. | | | | | |
| Ensure adequate IV hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10 ⁹ /L to reduce the risk of TLS. | | | | | |
| | OBINUTUZUMAB | 1000mg | IVI | See above | In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9% |
| TTO | Drug | Dose | Route | Directions | |
| | VENETOCLAX (available as 10mg, 50mg and 100mg tablets) | See administration details For escalation schedule. | PO | Continue titration dose: 50mg OD for 1 week then 100mg OD for 1 week then 200mg OD for 1 week then 400mg OD Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing. During dose titration the dose should be taken in the morning. | |
| | Metoclopramide | 10mg | PO | Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously. | |
| | Allopurinol | 300mg | PO | OD for the first 3 cycles based on clinical judgement of tumour burden eg WBC count, extent of lymphadenopathy Review if alternative anti-hyperuricaemic agent required. | |
| | Aciclovir | 400mg | PO | BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose) | |
| | Co-trimoxazole | 480mg | PO | TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose) | |
| Consider prophylactic anti-fungal | | | | | |

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Cycle 3-6 repeat every 28 days

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---------------|-------|--|--|
| Day 1 | Methylprednisolone | 80mg | IV | Over 15 min | In 100ml Sodium Chloride 0.9%. Infusion must be completed at least 1 hour prior to the obinutuzumab infusion. |
| | Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10 ⁹ /L | | | | |
| | Paracetamol | 1g | PO | STAT | Given at least 30 minutes before the obinutuzumab infusion. |
| | Chlorphenamine | 10mg | IV | Slow bolus over 1 min | |
| | Omit if patient tolerated previous obinutuzumab infusion. | | | | |
| Ensure adequate IV hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10 ⁹ /L to reduce the risk of TLS. | | | | | |
| | OBINUTUZUMAB | 1000mg | IVI | See above | In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9% |
| TTO | Drug | Dose | Route | Directions | |
| Day 1 | VENETOCLAX (available as 10mg, 50mg and 100mg tablets) | 400mg | PO | 400mg OD Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing. | |
| | Metoclopramide | 10mg | PO | Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously. | |
| | Allopurinol | 300mg | PO | OD for the first 3 cycles based on clinical judgement of tumour burden e.g. WBC count, extent of lymphadenopathy. Review if required. | |
| | Aciclovir | 400mg | PO | BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose) | |
| | Co-trimoxazole | 480mg | PO | TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose). | |
| | Consider prophylactic anti-fungal | | | | |

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Cycle 7-12: repeat every 28 days

| TTO | Drug | Dose | | Directions |
|-------|--|-------|----|--|
| Day 1 | VENETOCLAX (available as 10mg, 50mg and 100mg tablets) | 400mg | PO | 400mg OD Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing. |
| | Metoclopramide | 10mg | PO | Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously. |
| | Aciclovir | 400mg | PO | BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose) |
| | Co-trimoxazole | 480mg | PO | TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose). |
| | Consider prophylactic anti-fungal | | | |

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Obinutuzumab Monitoring Record: Day.... Cycle.....

| Time after start of administration | Actual time | Rate of infusion (ml/hr) [Calculations based on 250ml reconstitution volume] | B.P. (mmHg) | Pulse rate (beats/min) | Respiration rate (beats/min) | Temp (°C) |
|------------------------------------|-------------|--|----------------|---------------------------|---------------------------------|-----------|
| 0 – 15 mins | | | | | | |
| 16 – 30 mins | | | | | | |
| 31 – 45 mins | | | | | | |
| 46 – 60 mins | | | | | | |
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