Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

VENETOCLAX (high risk)

Regimen

- CLL – Venetoclax (high risk)

Indication

- Venetoclax is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation, and who are unsuitable for or have failed a B-cell receptor pathway inhibitor.

- Venetoclax is indicated for the treatment of adult patients with CLL in the absence of 17p deletion or TP53 mutation, and who are unsuitable for or have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

Toxicity

Drug	Adverse Effect
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 further details.

Monitoring

Drugs

- FBC, U&Es and LFTs on cycle one day 1, 2, 8, 9, 15, 16, 22, 23 and on cycle two day 2 (to include phosphate, calcium and LDH). These parameters must be checked prior to any dose increase. Consider on day 1 of subsequent cycles or refer to ocal guidelines.

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

- Viral screening is required before starting treatment including Hepatitis B surface antigen, core antibody and HIV status.

- FBC, U&Es (including postassium, 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.

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

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L).

Treatment with venetoclax should be withheld for grade 3 or 4 febrile neutropenia and/or infection, or other 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, the dose reduction guidelines in Table 2 should be followed when resuming treatment with venetoclax following recovery. A larger dose reduction may occur at the discretion of the physician. Discontinuation of venetoclax should be considered in patients who require dose reductions to less than 100 mg for more than 2 weeks

Hepatic Impairment

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

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, 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.

Tumour Lysis Syndrome

Venetoclax can cause a rapid reduction in tumour, and thus poses a risk for tumour lysis syndrome in the initial 5-week dose-titration phase. Changes in electrolytes consistent with

tumour lysis syndrome that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. It is strongly recommended to admit the patient for monitoring initially.

The risk of tumour lysis syndrome is a continuum based on multiple factors, including co-morbidities. Patients with high tumour burden (e.g., any lymph node with a diameter greater than or equal to 5cm or high absolute lymphocyte count greater than or equal to $25x10^9$/L) are at greater risk of tumour lysis syndrome when initiating venetoclax and should be treated as high risk. Reduced renal function (creatinine clearance less than 80ml/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment. Drug interactions may also contribute. Always check for drug interactions.

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase. These agents must not be prescribed together during this part of treatment.

Prior to initiating venetoclax, tumour burden assessment, including radiographic evaluation (e.g. CT scan), must be performed for all patients. Blood chemistry (potassium, uric acid, phosphate, adjusted calcium, LDH and creatinine) should be assessed and pre-existing abnormalities corrected. The prophylaxis measures listed below should be followed.

Patients should be adequately hydrated during the dose-titration phase. 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 tumour lysis syndrome or for those who cannot maintain an adequate level of oral hydration.

-For high risk patients the anti-hyperuricemic plan is rasburicase 7.5mg used prophylactically at initiation and for the first dose increase then start allopurinol before the third dose increase and continue until dose titration is complete. For low risk patients use separate protocol – initiate allopurinol two days before starting venetoclax and continue until dose titration is complete.

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

Abnormality	**Dose Modification and Management**
Hyperkalaemia	
Potassium more than or equal to 0.5mmol/l increase from prior value (and within upper limit of normal (ULN))	Hold venetoclax until resolution Recheck calcium, creatinine, phosphate, potassium and uric acid in 1hour. If further 0.2mmol/l or more rise in potassium do an ECG and consider calcium gluconate and calcium resonium in line with local hyperkalaemia policy. Continue to monitor for TLS every 2 hours Resume protocol testing if change in potassium is less than 0.2mmol/l and no other evidence of TLS resume venetoclax.
Potasssium more than ULN but less than 6.0mmol/l	Hold venetoclax until resolution Do an ECG and consider calcium gluconate and calcium resonium in line with local hyperkalaemia policy. Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour. If

Abnormality	Dose Modification and Management
	potassium less than ULN continue to monitor for TLS 2 and 4 hours later
Potassium more than or equal to 6.0mmol/l and/or symptomatic (e.g. muscle cramps, weakness, paraesthesia, nausea, vomiting or diarrhoea)	Hold venetoclax until resolution Refer to local hyperkalaemia guideline and seek advice from renal team. Recheck calcium, creatinine, phosphate, potassium and uric acid every hour
Hyperuricaemia	
Uric acid more than or equal to 476micromol/l	Hold venetoclax until resolution. Consider giving rasburicase if not given in last 24 hours.
Hypocalcaemia	
Adjusted calcium less than 1.75mmol/l or patient symptomatic (e.g. muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcaemia.	Hold 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 1.45mmol/l and less than 1.67mmol/l	Withold venetoclax until resolution Does not require treatment. Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour.
Phosphate 1.67 to 2.1mmol/L	Withold venetoclax until resolution to less than 1.45mmol/l Discuss with 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.
Phosphate more than 2.1mmol/l	Withold venetoclax until resolution to less than 1.45mmol/l Discuss with renal team as a phosphate binder or haemodialysis may be required. Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour.
Creatinine	
Increase of more than or equal to 25% from baseline.	Hold venetoclax until resolution Administer intravenous fluids. Recheck potassium, phosphate, uric acid, calcium and creatinine in 1 to 2 hours
LDH	
Increase of more than 50% from baseline	Hold venetoclax until level is back to baseline (check level weekly). Restart at previous dose level. If occurred on first dose restart at 10mg daily.

If biochemical changes suggestive of tumour lysis syndrome occur, the next venetoclax dose should be withheld and remainder of treatment dose 0.2mg/kg/day (less 7.5mg prophylactic dose) should be given. Blood electrolytes (potassium, phosphate, uric acid, calcium and creatinine) should be carefully monitored and responded to every 2 hours to assess TLS

response or progression until patient stable. If the changes resolve within 24 to 48 hours of the last dose, treatment with venetoclax can be resumed at the same dose.

If clinical tumour lysis syndrome or biochemistry changes occur, that require more than 48 hours to resolve, treatment should be resumed at a reduced dose (see table below). When resuming treatment with venetoclax after interruption due to tumour lysis syndrome, the instructions for prevention of tumour lysis syndrome should be followed.

Table 2 – Venetoclax dose modifications if resolution of TLS sign take more than 48hours

Dose modification for TLS and other toxicities during venetoclax treatment	
Dose at interruption (mg)	**Restart dose (mg[a])**
400	300
300	200
200	100
100	50
50	20
20	10
[a]The modified dose should be continued for 1 week before increasing the dose.	

Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in ARIA)

Cycle 1

This cycle will be set up on ARIA in 7 day blocks that can be prescribed independently

Drug	Dose	Days	Administration
Venetoclax	20mg*	1, 2, 3, 4, 5, 6, 7	Oral
	50mg*	8, 9, 10, 11, 12, 13, 14	
	100mg*	15, 16, 17, 18, 19, 20, 21	
	200mg*	22, 23, 24, 25, 26, 27, 28	

*Day 1, 8, 15 and 22 will be dispensed as a separate supply to allow evaluation for TLS on day 2, 9, 16 and 23

Cycle 2 onwards

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

*Day 1 of cycle two only will be dispensed as a separate supply to allow evaluation for TLS on day 2

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

- 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 Therapy

- Antiemetics

  As take home medication

  - metoclopramide 10mg three times a day when required oral

- Allopurinol 300mg once a day oral for 28 days oral starting on day 12 of cycle 1 to continue for 28 days.

- Calcium carbonate 1.5g or 1.25g (in line with local protocol) three times a day for 28 days oral starting on day 1 of cycle 1 only. Used as a phosphate binder to reduce the risk of dose delay due to hyperphosphataemia during the initial titration phase. Dose should be taken with food.

- Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes on cycle 1 days 1, 2, 8 and 9.

- 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. Additional 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.

- Sodium chloride 0.9% 1000ml over 4 hours to starting at least one hour prior to the administration of venetoclax on cycle 1 days 1 and 8. Advise patient to drink an additional litre of water during the day.

- Sodium chloride 0.9% 500ml over 2 hours starting at least one hour before administration of venetoclax on cycle 1 days 2 and 9.

- 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 must 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.

Coding

- Procurement – X71.5

- Delivery – X73.1

References

1.Abbvie Limited (2016) Venetoclax film-coated tablets Summary of Product Characteristics. Online at http://www.medicines.org.uk/emc/medicine/32650, accessed 16 January 2017.
2.Roberts AW, Davids MS, Pagel JM et al. (2016) Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. New Engl J Med (2016): **374** (4); 311-22
3.Preston CL (ed), Stockley's Drug Interactions. London: Pharmaceutical Press. Online at https://www.medicinescomplete.com, accessed 16 January 2016.
4. Wessex Blood and Marrow Transplant Tumour Lysis Prevention and Management Policy (Adults) version 1.0

REGIMEN SUMMARY

Venetoclax (high risk)

Cycle 1

Day 1

1. Warning – Check in-patient administration
   Administration Instructions
   If the patient has been admitted for monitoring please check what was prescribed and administered either on the in-patient electronic or / and paper system and adjust this prescription accordingly. This prescription is designed for out-patient use and may not be used for an in-patient.

2. Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
   Administration Instruction
   Administer after baseline blood sample has been taken

3. Sodium chloride 0.9% 1000ml intravenous infusion over 240 minutes
   Administration Instruction
   Advise patient to drink an additional litre of water during the day. 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

4. Warning – Administer venetoclax
   Administration Instructions
   Administer venetoclax as per the dosage in the take home medicines, please record the time of administration by administering this warning in ARIA. This is to facilitate the diagnosis of TLS from the blood results. Administer the venetoclax at least one hour after the start of the sodium chloride 0.9% infusion. Ensure all the correct blood tests have been taken at the correct time.

   Take with or after food. Take with a full glass of water.

   Oral chemotherapy.

Take Home Medicines (day 1)

5. Venetoclax 20mg once a day for 1 day oral
   Administration Information
   Administer 20mg once a day on day 1 only, please record the time of administration by administering the “warning – administer venetoclax” in ARIA. This is to facilitate the diagnosis of TLS from the blood results. Administer the venetoclax one hour after the start of the sodium chloride 0.9% infusion. Ensure all the correct blood tests have been taken at the correct time.

   Dispense only one dose

   Take with or after food. Take with a full glass of water.

   Oral chemotherapy

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

7. Calcium carbonate One tablet three times a day oral
   Administration instructions
   Take with or after food. This is being used as a phosphate binder, it is essential it is taken with meals
   Please dispense an original pack as per local formulary eg;calcium carbonate 1.25g or calcium carbonate 1.5g

Day 2

8. Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

9. Sodium chloride 0.9% 500ml intravenous infusion over 120 minutes
   Administration Instruction
   Advise patient to drink an additional 1.5 litres of water during the day.

Take Home Medicines (day 2 only)

10. Venetoclax 20mg once a day for 6 days oral
    Administration Information
    Start on day 2 of the cycle. Dispense six days only.

    Take with or just after food. Take with a full glass of water.

    Oral chemotherapy

Day 8

11. Warning – Check in-patient administration
    Administration Instructions
    If the patient has been admitted for monitoring please check what was prescribed and administered either on the in-patient electronic or / and paper system and adjust this prescription accordingly. This prescription is designed for out-patient use and may not be used for an in-patient.

12. Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
    Administration Instruction
    Administer after baseline blood sample has been taken

13. Sodium chloride 0.9% 1000ml intravenous infusion over 240 minutes
    Administration Instruction
    Advise patient to drink an additional litre of water during the day. 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.

14. Warning – Administer venetoclax
    Administration Instructions
    Administer venetoclax as per the dosage in the take home medicines, please record the time of administration by administering this warning in ARIA. This is to facilitate the diagnosis of TLS from the blood results. Administer the venetoclax at least one hour after the start of the sodium chloride 0.9% infusion. Ensure all the correct blood tests have been taken at the correct time.

    Take with or after food. Take with a full glass of water.

    Oral chemotherapy

Take Home Medicines (day 8)

15. Venetoclax 50mg once a day for 1 day oral
    Administration Information
    Administer 50mg once a day on day 8 only, please record the time of administration by administering the "warning – administer venetoclax" in ARIA. This is to facilitate the diagnosis of TLS from the blood results. Administer the venetoclax one hour after the start of the sodium chloride 0.9% infusion. Ensure all the correct blood tests have been taken at the correct time.

    Dispense only one dose

    Take with or after food. Take with a full glass of water

    Oral chemotherapy

Day 9

16. Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

17. Sodium chloride 0.9% 500ml intravenous infusion over 120 minutes
    Administration Instruction
    Advise patient to drink an additional 1.5 litres of water during the day

Take Home Medicines (day 9 only)

18. Venetoclax 50mg once a day for 6 days oral
    Administration Information
    Start on day 9 of the cycle. Dispense 6 days only.

    Take with or just after food. Take with a full glass of water.

    Oral chemotherapy

19. Allopurinol 300mg once a day for 28 days oral
    Administration information
    Start on day 12 of the cycle.

Day 15

20. Warning - Administer venetoclax
    Administration Instructions
    Administer venetoclax as per the dosage in the take home medicines, please record the time of administration by administering this warning in ARIA. This is to facilitate the diagnosis of TLS from the blood results.
    Ensure all the correct blood tests have been taken at the correct time and that the patient is drinking a minimum of 2 liters of fluid a day.

    Take with or after food. Take with a full glass of water.

    Oral chemotherapy

Take Home Medicines (Day 15 only)

21. Venetoclax 100mg once a day for 1 day oral
    Administration information
    Administer 100mg once a day on day 15 only. If appropriate please record the time of administration in the journal in ARIA. This is to facilitate the diagnosis of TLS from the blood results. Ensure all the correct blood tests have been taken at the correct time.

    Dispense only one dose

    Take with or after food. Take with a full glass of water

    Oral chemotherapy

Take Home Medicines (Day 16 only)

22. Venetoclax 100mg once a day for 6 days oral
    Administration Information
    Start on day 16 of the cycle. Dispense 6 days only.

    Take with or just after food. Take with a full glass of water.

    Oral chemotherapy

Day 22

23. Warning - Administer venetoclax
    Administration Instructions
    Administer venetoclax as per the dosage in the take home medicines, please record the time of administration by administering this warning in ARIA. This is to facilitate the diagnosis of TLS from the blood results.
    Ensure all the correct blood tests have been taken at the correct time and that the patient is drinking a minimum of 2 liters of fluid a day.

    Take with or after food. Take with a full glass of water.

Take Home Medicines (Day 22 only)

24. Venetoclax 200mg once a day for 1 day oral
    Administration information
    Administer 200mg once a day on day 22 only. If appropriate please record the time of administration in the journal in ARIA. This is to facilitate the diagnosis of TLS from the blood results. Ensure all the correct blood tests have been taken at the correct time.

    Dispense only one dose

    Take with or after food. Take with a full glass of water

    Oral chemotherapy

Take Home Medicines (Day 23 only)

25. Venetoclax 200mg once a day for 6 days oral
    Administration Information
    Start on day 23 of the cycle. Dispense 6 days only.

    Take with or just after food. Take with a full glass of water.

    Oral chemotherapy

Cycle 2

Day 1

26. Warning - Administer venetoclax
    Administration Instructions
    Administer venetoclax as per the dosage in the take home medicines, please record the time of administration by administering this warning in ARIA. This is to facilitate the diagnosis of TLS from the blood results.
    Ensure all the correct blood tests have been taken at the correct time and that the patient is drinking a minimum of 2 liters of fluid a day.

    Take with or after food. Take with a full glass of water.

    Oral chemotherapy

Take Home Medicines (Day 1 only)

27. Venetoclax 400mg once a day for 1 day oral
    Administration Information
    Administer 400mg once a day on day 1 only. If appropriate please record the time of administration in the journal in ARIA. This is to facilitate the diagnosis of TLS from the blood results. Ensure all the correct blood tests have been taken at the correct time.

    Dispense only one dose

    Take with or after food. Take with a full glass of water

    Oral chemotherapy

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

Take Home Medicines (Day 2 only)

29. Venetoclax 400mg once a day for 27 days oral
    Administration Information
    Start on day 2 of the cycle. Take with or just after food.

    Take with a full glass of water.

    Oral chemotherapy

Cycle 3 onwards

Take Home Medicines (Day 1 only)

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

   Oral chemotherapy

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	November 2018	Update to process of tumour lysis symptom prevention, identification and management	Harriet Launders Pharmacist	Dr Andrew Duncombe Consultant Haematologist
1	February 2017	None	Eleanor Taylor Pharmacist	Dr Andrew Duncombe 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 should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.