MATRix

[High-dose Methotrexate, high-dose Cytarabine (Ara-C), Thiotepa, Rituximab]

INDICATION

Licensed* / NHSE funded: **CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA** [ICD-10 codes: C83, C85]

Omit rituximab for CD20 negative lymphoma

*Note: Thiotepa is used off-label. Ensure compliance with local Trust's governance framework.

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Ensure histology is confirmed and documented in the notes. Although it is sometimes difficult to obtain tissue in cases of primary CNS lymphoma, treatment should NOT be given without this.
2. Record stage and IPI of disease - CT scan (neck, chest, abdomen and pelvis) or PET-CT, presence or absence of B symptoms, clinical extent of disease. Consider bone marrow aspirate and trephine.
3. Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, vitamin D level, magnesium, creatinine, LFTs, glucose, HbA1c, Igs, β2 microglobulin, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, EBV, CMV, VZV, HIV, HTLV-1, glucose 6-phosphate dehydrogenase (G6PD) when indicated [H.8], group and save. **Note**: The risk of primary CNS lymphoma is raised several thousand fold by the presence of HIV infection.
4. Assess **renal function** (Wright GFR) and the risk of methotrexate (MTX) nephrotoxicity. Consider directly measuring GFR (NM GFR), using, for example, ^{99m}Tc-DTPA to assess baseline renal function, especially in patients with pre-existing renal impairment, extremes of body weight and other co-morbidities. When it is impractical to obtain NM GFR and / or GFR is < 80mL/min, discuss MTX dose with Consultant and the benefits versus risks of proceeding with treatment. If off-label use is required, follow appropriate Trust governance processes [see DOSE MODIFICATIONS below].
5. Assess any pathologic **fluid accumulation (third space fluids) such as ascites or pleural effusions** that may lead to prolonged methotrexate plasma elimination and unexpected toxicity. High dose methotrexate should not be given in such cases, and therefore pleural effusions and ascites should be drained prior to initiation of methotrexate treatment.
6. Confirm **medication history** and check for any **drugs** that can inhibit renal tubular secretion of MTX. These mainly include co-trimoxazole, penicillins, aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Proton Pump Inhibitors (PPIs). Counsel patients to **stop co-trimoxazole** in the week before the first high dose methotrexate (MTX) infusion. Switch to pentamidine as alternative Pneumocystis jiroveci pneumonia (PJP) prophylaxis during MTX treatment. Co-trimoxazole can be restarted after the last cycle of high dose MTX, once the MTX level is below 0.1 micromol/L and adequate neutrophil count recovery is achieved. NSAIDs and penicillin antibiotics should also be avoided before and during methotrexate infusion. **Tazocin should NOT be used** during high dose methotrexate administration or rescue – use an alternative as per local formulary and antibiotic guidelines. Review indications for aspirin, NSAIDs and PPIs and consider stopping during MTX treatment and prescribing alternative if required (see DRUG INTERACTIONS below).
7. Assess **cardiac function**, ECG +/- ECHO - if clinically indicated.

8. Record performance status [ECOG] and cognitive state including MMS.
9. Record vital signs, height and weight.
10. Record the prognostic score. 1 point for each: age > 60 years, ECOG performance status > 1, raised serum LDH, raised CSF protein, deep brain structures involved.
11. Consider lumbar puncture to ascertain for the presence of leptomeningeal involvement by flow cytometry and CSF protein (raised level is a poor prognostic factor). **Note**: Contraindicated in the presence of space occupying lesion associated with raised intracranial pressure.
12. MRI brain with gadolinium to accurately ascertain extent of disease (multiple lesions and deep lesions represent poor prognostic features).
13. Consider testicular ultrasound in older men.
14. Slit lamp examination of both eyes. If presence of intraocular disease confirmed, consider radiotherapy to orbits at the end of treatment.
15. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or had a hysterectomy.
16. Consent and counselling - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. **Advise patients to take precautions in the sun to avoid photosensitivity reactions** [MHRA Drug Safety Update]. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
17. Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
18. Assess and document **tumour lysis syndrome (TLS) risk** as part of pre-assessment. Patients should be adequately hydrated before and after each cycle administration. **In bulky disease pre-hydrate with sodium chloride 0.9%** 1 litre over 4-6 hours. Refer to the TLS protocol [H.8].
19. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
20. Start hydration and urine alkalinization with sodium bicarbonate at T= -12 hours. T= 0 is the start time of methotrexate infusion (see DRUG REGIMEN below). Dipstick urine every 2 hours to check pH is maintaned ≥ 7. **If pH < 7, give additional sodium bicarbonate as required.** Review regular sodium bicarbonate requirements at the end of the methotrexate infusion, and continue as appropriate until methotrexate level < 0.1 micromol/L.
21. Methotrexate infusion should be administered over 3 hours 15 minutes, although it may be extended if technical issues restrict the flow rate.
22. Intrathecal chemotherapy is **NOT** a part of this regimen.
23. Treatment should be agreed in the relevant MDT.

When MATRix regimen is used for priming and harvesting:

1. Liaise with BMT nurse co-ordinator for timing of harvest and possible transplant slot.
2. **Stem cell collection should be performed on days 13, 14 & 15 of the cycle.**
3. **Aim to collect 4.0x10^6 CD34-positive cells/kg [minimum of 2.0x10^6 CD34-positive cells/kg].**
4. Venous access should be assessed well in advance of collection. Every effort should be made not to use antecubital fossa veins in the run up to harvest.
5. If good antecubital fossa veins, insert power PICC. Apheresis line to be inserted if poor antecubital veins.
6. Ensure the peripheral stem cell harvest / final donor clearance form (FRM3721) is sent within 30 days of scheduled harvest date to NHSBT, to confirm eligibility for PBSCH.
7. **Infective agent screen.** Peripheral blood stem cells for autologous transplant are cryopreserved in liquid nitrogen. In order to eliminate the risk of transmitting infective agents during the storage of marrow, virology testing is mandatory within 30 days of the harvesting procedure and results must be known before priming. Bottles and consent form provided by NHSBT Oxford. Please send to the NHSBT stem cell laboratory in Oxford. Address is provided on the consent form.

DRUG REGIMEN

Day(s)	Time [hrs]	Drug	Dose	Route	Administration details
0, 1		Paracetamol Hydrocortisone Chlorphenamine	1000 mg 100 mg 10 mg	PO IV IV	≥ 30 minutes before rituximab
0, 1		**RITUXIMAB**	**375 mg/m²**	**IV**	In 500 mL sodium chloride 0.9%*
1	-12	Hydration & urine alkalinization pre MTX			See **Table 1**, page 4
2	0	**METHOTREXATE**	**500 mg/m²**	**IV**	First dose of MTX: in exactly 100 mL sodium chloride 0.9% **over 15 minutes**
2	0 +15min	**METHOTREXATE**	**3000 mg/m²**	**IV**	Second dose of MTX (commence immediately after the first dose): in exactly 500 mL sodium chloride 0.9% **over 3 hours**
2	+3	Hydration & urine alkalinization post MTX			See **Table 1**, page 4
3	+24	Calcium folinate (folinic acid) post MTX			See **Table 1**, page 4
3, 4	+24,36 48,60	**CYTARABINE**	**2000 mg/m²** **TWICE daily**	**IV**	In 250 mL sodium chloride 0.9% over 1 hour
5		**THIOTEPA**	**30 mg/m²**	**IV**	In 100 mL sodium chloride 0.9% [or, in 50 mL sodium chloride 0.9% for thiotepa doses < 50 mg] over 30 minutes **via 0.22micron filter**
CYCLE FREQUENCY: every 21 days					
TREATMENT DURATION: 4 cycles					

* Refer to [Nursing Care Plans: Rituximab infusion rates], max. rate 400 mg/hour]. Patients should be observed for 30 minutes before the start of other infusions. If first dose is well tolerated, consider rapid infusion rituximab rate from cycle 2 onwards.

CONCURRENT MEDICATIONS

Hydration and urine alkalinization pre-& post-MTX / Calcium folinate – see **Table 1**, page 4.		
TLS prophylaxis		Hydration + allopurinol 300mg OD [reduced dose in renal impairment] for 7 days [cycle 1] unless otherwise indicated in the Tumour Lysis Syndrome in Adults protocol [H.8].
Antiviral prophylaxis		Aciclovir 200mg TDS during treatment and for 3 months after completion
PJP prophylaxis		Pentamidine 4mg/kg IV infusion once a month (max. 300mg) [avoid co-trimoxazole – see INTERACTIONS below]
Antifungal prophylaxis		Fluconazole 50mg OD for the duration of treatment
Cytarabine-induced conjunctivitis prophylaxis		Steroid eye drops, as per local formulary, for example, prednisolone 0.5% (Minims) or dexamethasone 0.1%. One drop to each eye QDS from day 3 and continue for 5 days after last cytarabine dose. In the event of conjunctivitis, consider increasing the frequency to 2 hourly until resolution of symptoms. Consult with Ophthalmologists as appropriate.
G-CSF	**Non-priming cycles**	Filgrastim **0.5 MU/kg/day**, starting **from day 9** for 7 days
	Priming cycle	Filgrastim **1.0 MU/kg/day**, starting **from day 6** until stem cell harvest [provide 10-day supply].
Anti-emetics Days 0 and 1: Minimal risk Days 2–4: Moderate risk Day 5: Low risk		▪ Ondansetron on days 2-4: 8mg BD ▪ Metoclopramide on days 2-7: 10-20mg TDS. For breakthrough nausea or vomiting: 10-20mg TDS when required. For alternative options, refer to [TVCA Anti-emetic guideline].
Gastric protection*		Famotidine 20mg BD [avoid PPIs – see INTERACTIONS below]

(*) indicates optional concurrent medications

Table 1. High-dose Methotrexate (HD MTX) toxicities prophylaxis and management

<table>
<tr><td>Pre-hydration and urine alkalinization</td><td>▪ Start 12 hours before methotrexate (MTX) infusion.
▪ IV continuous infusion: 1000 mL Glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and sodium bicarbonate 100 mmol. Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6 m^2). Duration: continuous infusion for 15 hours 15 minutes (run concurrently with the MTX infusion). PO: Sodium bicarbonate 1500 mg four times daily + 1500 mg 2-hourly when required.
▪ Dipstick urine every 2 hours to check if pH ≥ 7. If pH under 7, give additional sodium bicarbonate (PO) 1500 mg.</td></tr>
<tr><td>Urine output</td><td>▪ Check every 4 hours. Aim: 400 mL/m^2/4 hours (approximately 700 mL over 4 hours). Furosemide: Administer 20-40 mg when required to maintain urine output.</td></tr>
<tr><td>Post-hydration and urine alkalinization</td><td>▪ Start immediately at the end of MTX infusion.
▪ IV continuous infusion: 1000 mL Glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and sodium bicarbonate 50 mmol. Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6 m^2). Duration: continuous infusion until MTX level < 0.1 µmol/L. PO: Sodium bicarbonate 1500 mg four times daily + 1500 mg 2-hourly when required.
▪ Dipstick urine every 2 hours to check if pH ≥ 7. If pH under 7, give additional sodium bicarbonate (PO) 1500 mg.
▪ Review the need for regular sodium bicarbonate at the end of MTX infusion and continue as appropriate until MTX levels < 0.1 µmol/L.</td></tr>
<tr><td>Calcium folinate (folinic acid)</td><td>▪ Start 24 hours after the start of MTX infusion: 15 mg/m^2 IV every 3 hours for 5 doses, then 15 mg/m^2 IV/PO* every 6 hours until MTX levels < 0.1 µmol/L
▪ Based on plasma MTX levels and after discussing with the Consultant, calcium folinate dose may need adjustment as below.
<table>
<tr><th colspan="4">Calcium folinate (folinic acid) dose adjustments
according to plasma MTX levels after 48 hours from the start of MTX infusion</th></tr>
<tr><th>Plasma MTX level</th><th>< 0.5 µmol/L</th><th>0.5–1 µmol/L</th><th>> 1 µmol/L</th></tr>
<tr><td>Calcium folinate dose</td><td>15 mg/m^2 PO*/IV every 6 hours</td><td>50 mg/m^2 IV every 6 hours</td><td>100 mg/m^2 IV every 6 hours</td></tr>
</table>
* PO tablets may only be given if the patient is not nauseous/vomiting and dose is ≤ 30 mg as the tablet bioavailability greatly decreases with the higher doses.
▪ Calcium folinate 100 mg/m^2 IV 6 hourly should also be administered in patients with toxic plasma MTX levels > 20 µmol/L after 24 hours or until the MTX level is known following MTX overdose, or in patients with clinical features of MTX toxicity (e.g. mucositis, signs of bone marrow suppression, hepatotoxicity or renal dysfunction).
▪ Due to the large quantities of calcium, the infusion time of calcium folinate at doses > 200–500 mg (or the patient's body surface area (BSA) × 50) should be over 1–2 hours. Monitor calcium concentrations closely.</td></tr>
<tr><td>Glucarpidase</td><td>▪ Consider early glucarpidase in MTX induced renal dysfunction (> 1.5 x baseline and rising, or the presence of oliguria) and presence of toxic plasma MTX levels: > 20 µmol/L after 24 hours or > 5 µmol/L after 48 hours from the start of MTX infusion, despite rescue measures, which might be life-threatening.
▪ Administration of glucarpidase should optimally occur within 60 hours from the start of MTX infusion, because life-threatening toxicities may not be preventable beyond this time point. Clinical data however show that glucarpidase continues to be effective beyond this time window. Folinic acid should not be administered within 2 hours before or after glucarpidase administration to minimise any potential interaction. In the absence of more specific HPLC assay, the dose of folinic acid used in a 48 hour-period after glucarpidase should be based on the MTX concentration from a sample taken prior to glucarpidase administration.
▪ The recommended dose is one single intravenous injection of 50 units/kg. Multiple doses are not permitted. Blueteq required. Refer to [NHSE Glucarpidase policy] and [TVCA Glucarpidase guideline] for more details.</td></tr>
</table>

CONTRAINDICATIONS

Refer to individual Summary of Product Characteristics (SmPC) for full details. Leptomeningeal involvement, severe active infection, hypersensitivity to drugs in the regimen. High-dose MTX: renal impairment [see DOSE MODIFICATIONS below], severe liver impairment, ascites or pleural effusions.

INVESTIGATIONS

- FBC, U&Es, LFTs, magnesium, calcium, phosphate, urea
- Weight, vital signs, pH to maintain ≥ 7.
- Plasma **MTX levels** starting **from 24 hours after the start of MTX infusion**, then **every 24 hours.**
- CXR as clinically indicated.

RESTAGING

Clinical response should be assessed on a monthly basis.
Repeat MRI brain after 2 cycles and 4 cycles.

TREATMENT MODIFICATIONS

All dose modifications must be discussed with the Consultant.

Note: in the IELSG32 trial, all patients were ≤ 70 years of age[1]

For patients > 70, who are deemed fit for intensive therapy, consider reducing doses in the following order:

- Reduce cytarabine dose to 50% by omitting 2 doses of cytarabine on Day 4
- Reduce thiotepa dose to 75%
- Reduce methotrexate to 2000 mg/m^2

Haematological toxicities

In case if inadequate bone marrow recovery (i.e. neutrophils < 1.5 x 10^9/L and platelets < 90 x 10^9/L on the intended day of treatment, delay cycle until counts satisfactory.

Doses of the chemotherapy drugs in subsequent cycles are determined according to nadir neutrophil or platelet count of the previous cycle as follows:

Nadir neutrophils (x10^9/L)	Dose modifications	Nadir platelets (x10^9/L)	Dose modifications
≥ 0.5	Unchanged	≥ 25	Unchanged
< 0.5	Reduce cytarabine to 75% (by omitting 4th dose)	< 25	Reduce cytarabine to 75% (by omitting 4th dose) AND reduce thiotepa to 75%

Non-haematological toxicities

For grade 3-4 non-haematological, non renal / liver toxicities, the next cycle should be delayed until the grade of toxicity is 2 or less. The subsequent cycle should then be administered as follows:

Toxicity	Grade 3	Grade 4
Cardiovascular	Interruption	Interruption
Coagulation	Unchanged	Reduce MTX, Ara-C and Thiotepa to 75%
Gastrointestinal	Unchanged	Reduce MTX, Ara-C and Thiotepa to 75%
Pulmonary	Unchanged	Reduce MTX, Ara-C and Thiotepa to 75%

Renal / Hepatic Impairment

GFR (Glomerular Filtration Rate) = estimated using Wright formula (Wright GFR), or measured using isotopic filtration markers, for example, ^{99m}Tc-DTPA or ^{51}Cr-EDTA (NM GFR).

NM GFR [uncorrected] should be considered at extremes of body weight and based on individual patient clinical context (age, co-morbidities). When impractical to obtain NM GFR, discuss alternative methods to assess renal function with the Consultant.

	Renal impairment	Hepatic impairment
Methotrexate	GFR ≥ 80 mL/min: 100% dose GFR 50-79 mL/min: 100% dose, or consider dose reduction (see below*) GFR < 50 mL/min: omit	Mild and moderate: caution required, consider dose reduction or discontinue with concomitant renal impairment or constant increase in liver enzymes – clinical decision (see below**). Severe: avoid use
Cytarabine	GFR ≥ 60 mL/min: 100% dose GFR 31-59 mL/min: 50% dose GFR ≤ 30 mL/min: omit	Mild and moderate: 100% dose Severe: consider 25–50% dose and increase if tolerated
Thiotepa	GFR ≥ 30 mL/min: 100% dose GFR < 30 mL/min: consider 70% dose, increase if tolerated – caution is recommended.	Bilirubin < 1.5 x ULN: 100% dose Bilirubin 1.5–3 x ULN: 100% dose with intensified monitoring Bilirubin > 3 x ULN: not recommended

* Discuss with Consultant whether to proceed with a full MTX dose to maintain dose intensity for optimal treatment outcomes, or consider dose reduction in individual patients, especially those with poorer performance status and/or co-morbidities. Consult Nephrology when appropriate. Note off-label use when a full dose is administered for GFR < 80 mL/min and any dose for GFR < 60 mL/min (refer to SmPC for full details). If off-label use is required, follow the appropriate Trust governance processes. If dose reduction is required, it will only apply to the MTX dose administered over 3 hours.

** Patients receiving high dose methotrexate may develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to 2 weeks following the methotrexate infusion and are not considered toxicity requiring discontinuation of repeated administration of methotrexate. Persistent hyperbilirubinemia and/or grade 3-4 hypertransaminasemia for longer than 3 weeks should result in discontinuation of the drug.

DRUG INTERACTIONS

Rituximab	▪ Since hypotension may occur during rituximab administration, consider withholding anti-hypertensive medication(s) 12 hours prior to rituximab infusion.
Methotrexate	▪ Co-trimoxazole: avoid concomitant use. Acute megaloblastic pancytopenia, probably due to additive inhibition of the dihydrofolic acid reductase can occur. Co-trimoxazole should be stopped a week before the start of MTX and held until neutrophil count recovery and MTX levels < 0.1 micromol/L after last cycle. ▪ Penicillins: avoid concomitant use. Reduced renal clearance of methotrexate can occur. Tazocin (piperacillin with tazobactam) should NOT be used during high dose methotrexate administration until methotrexate levels < 0.1 micromol/L – use an alternative as per local formulary and antibiotic guidelines. ▪ NSAIDs and salicylate: avoid concomitant use. Severe (including fatal) bone marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage). ▪ Proton pump inhibitors: avoid concomitant use. Delayed elimination and increased serum methotrexate can occur.
Thiotepa	▪ Use with caution with CYP2B6 and CYP3A4 inhibitors.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- **Rituximab** may cause patient chillness, fever, headache, tiredness, aching muscles and joints, itching redness of skin, nausea and mild drop in blood pressure. **Hepatitis B reactivation** – see pathway for treatment and management of HBV positive patient [LPW.21].
- **Methotrexate:** renal damage, hepatotoxicity, interstitial pneumonitis (cough, dyspnoea, fever), stomatitis, diarrhoea, skin changes and increased skin sensitivity to sun, gritty eyes, hair loss, neurotoxicty including headache, dizziness, blurred vision and loss of balance.

  Photosensitivity reactions – refer to [MHRA advice for healthcare professionals]
  - Known side effect of MTX that can occur with both low-dose and high-dose treatment.
  - Reactions manifest as severe sunburn such as rashes with papules or blistering, with some patients reporting swelling; rarely, photosensitivity reactions contributed to deaths from secondary infections.
  - Healthcare professionals, including those prescribing and dispensing methotrexate: remind patients to take precautions to protect themselves from the sun and UV rays. Suspected adverse drug reactions associated with methotrexate should be reported via [MHRA Yellow Card].
- **High dose cytarabine:** nausea, diarrhoea, oral ulceration, hepatic dysfunction, neuropathy, pulmonary toxicities, cardiomyopathy, ocular toxicities. **"Cytarabine syndrome"** is recognised toxicity, in which patients suffer from: fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 to 12 hours following administration. Cerebellar toxicity is also a recognised, albeit rare, side effect of high dose cytarabine.
- **Thiotepa:** myelosuppression, nausea and vomiting, reduced fertility, **skin reactions**. Horn et al. found elevated levels of thiotepa in gauze containing sweat and occluded and nonoccluded skin, suggesting that thiotepa is excreted onto the skin by sweat, providing potential mechanism for skin toxicity. It is therefore important to protect both the patient and health professionals from exposure[13].

EXTRAVASATION RISK

Rituximab: neutral
Methotrexate: inflammatory agent
Cytarabine: neutral
Thiotepa: neutral

TREATMENT RELATED MORTALITY

2–5%

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
Dr Graham Collins, Haematology Consultant	New document	May 2016	1.0	May 2018
	Harvesting recommendations added	July 2017	1.1	May 2018
Cheuk-kie Jackie Cheung, Haematology Pharmacist	Timing of MTX levels updated	May 2018	1.2	May 2020
Faouzi Djebbari, Haematology Pharmacist	Dose modifications, concurrent medications updated	August 2020	1.3	May 2022
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist, Dr Joe Browning, Consultant Haematologist, NSSG Lymphoma Group	Methotrexate high-dose toxicity prophylaxis and management [calcium folinate and glucarpidase advice updated]; Dose modifications updated; General formatting. Annual protocol review	July 2023	2.0	July 2025
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist	Restaging, investigations, contraindications, adverse effects, references updated. General formatting.	February 2024	2.1	February 2026
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist NSSG Lymphoma & CLL Group	Pre-assessment, adverse reactions & interactions updated. MHRA advice on photosensitivity reactions added. Drug regimen: MTX split dose included to increase CNS penetration. MTX toxicity prophylaxis and management [calcium folinate and glucarpidase advice updated; timing to check first MTX levels amended to 24 hours post MTX infusion]. Concurrent medications, MTX dose modifications (renal impairment) and references updated. General formatting. Annual protocol review.	September 2024	3.0	September 2026
		January 2025	3.1	September 2026
Natalia Czub, Advanced Haematology Pharmacist	Antiemetics section updated.	March 2025	3.2	September 2026