

# R-CODOX-M / R-IVAC

[Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Ifosfamide, Etoposide, Cytarabine]

## INDICATION

Licensed / NHS funded: **LARGE B-CELL LYMPHOMA** [ICD-10 codes: C83, C85]

- Burkitt lymphoma, 'double or triple hit' lymphoma or high IPI diffuse large B-cell lymphoma, particularly with high risk of CNS relapse.

## TREATMENT INTENT

Curative

## PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage and IPI of disease - MRI scan of brain (+/- spinal cord) with Gadolinium enhancement, CT scan (neck, chest, abdomen and pelvis) +/- PET, presence or absence of B symptoms, clinical extent of disease. Consider bone marrow aspirate and trephine (with cytogenetics/FISH as indicated).
3. Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, vitamin D level, magnesium, creatinine, LFTs, glucose, HbA1c, Igs,  $\beta$ 2 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.
4. Assess **glycaemic control** as steroids in this regimen can increase the risk of hyperglycaemia. All patients should have a baseline HbA1c and venous plasma glucose checked prior to commencing treatment, followed by venous plasma glucose checked at each cycle and antidiabetic medications managed according to local policies and the UK Chemotherapy Board and Joint British Diabetes Societies for Inpatient Care [JBDS-IP] guideline.
5. Assess **renal function** (Wright GFR) and the risk of Methotrexate (MTX) nephrotoxicity. Consider directly measuring GFR (NM GFR), using, for example,  $^{99m}\text{Tc}$ -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 and the benefits versus risks of proceeding with treatment with the Consultant. If off-label use is required, follow appropriate Trust governance processes (see DOSE MODIFICATIONS).
6. Assess any pathologic **fluid accumulation (third space fluids) such as ascites or pleural effusions** that may lead to prolonged MTX plasma elimination and unexpected toxicity. High dose MTX should not be given in such cases, and therefore pleural effusions and ascites should be drained prior to initiation of MTX treatment.
7. 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 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 MTX administration or rescue – use 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).

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8. Assess **cardiac function**, ECG +/- ECHO - if clinically indicated.
9. Cerebrospinal fluid (CSF) examination - cell count +/- immunophenotype, protein and glucose: can be done as part of 1<sup>st</sup> intrathecal.
10. Ophthalmic examination - if clinically indicated.
11. Record performance status [ECOG].
12. Record vital signs, height and weight.
13. 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.
14. 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.
15. 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.
16. 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 TLS protocol [H.8].
17. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
18. Arrange insertion of double lumen central line (or a PICC line) if possible.
19. 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 maintained  $\geq 7$ . **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.
20. Methotrexate infusion should be administered over **exactly 24 hours**: the **loading dose over 1 hour**, followed by the **remaining dose over 23 hours**.
21. **INTRATHECAL injections** must be administered according to the **national guidance and local intrathecal policy**.
22. **This protocol is usually delivered in an inpatient setting. R-IVAC regimen can be used in ambulatory setting for patient(s) meeting the criteria.** Refer to the local **Ambulatory Care Operational Policy**.
23. Treatment should be agreed in the relevant MDT.

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## DRUG REGIMEN

**HYDRATION** – ensure patient has a fluid input of **> 3 litres**, supplement intravenously as necessary.

- **Low-risk disease:** treatment consists of **R-CODOX-M regimen only** (3 cycles)  
Patients in the low-risk group must meet at least 3 of the following criteria:
  - Normal lactate dehydrogenase (LDH) level
  - ECOG performance status 0-1
  - Ann Arbor stage I or II
  - No more than 1 extranodal site (e.g., bone marrow, gastrointestinal tract, or CNS)
- **High risk disease:** treatment consists of **alternating R-CODOX-M** (2 cycles) **with R-IVAC regimen** (2 cycles) (4 cycles in total)  
Patients in the high-risk group must meet at least 2 of the following criteria:
  - Raised LDH level
  - ECOG performance status 2-4
  - Ann Arbor stage III or IV
  - More than 1 extranodal site

Each regimen consists of the **intrathecal injections**, which dates may need adjustment to ensure they are administered on weekdays only, depending on when each regimen starts – discuss with the Consultant.

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R-CODOX-M					
Low-risk disease: CYCLES 1 to 3 OR High-risk disease: CYCLES 1 and 3 (alternating with R-IVAC)					
Day(s)	Time [hrs]	Drug	Dose	Route	Administration details
1		Paracetamol Dexamethasone* Chlorphenamine	1000 mg 12 mg 10 mg	PO PO/IV IV	≥ 30 minutes before Rituximab
1		<b>RITUXIMAB</b>	<b>375 mg/m<sup>2</sup></b>	IV	In 500 mL sodium chloride 0.9%**
1		<b>DOXORUBICIN</b>	<b>40 mg/m<sup>2</sup></b>	IV	Bolus injection
1 & 8		<b>VINCRIStINE</b>	<b>1.5 mg/m<sup>2</sup></b> (max. 2 mg***)	IV	In 50 mL sodium chloride 0.9% over 10 minutes
1		<b>CYCLOPHOSPHAMIDE</b>	<b>800 mg/m<sup>2</sup></b>	IV	Bolus injection
2 & 4		<b>CYTARABINE</b>	<b>70 mg</b>	IT	<b>INTRATHECAL</b> injection
2–5		<b>CYCLOPHOSPHAMIDE</b>	<b>200 mg/m<sup>2</sup></b>	IV	Bolus injection
9	-12	Hydration & urine alkalinization pre-Methotrexate			See Table 1, page 4
10	0	<b>METHOTREXATE</b>	<b>300 mg/m<sup>2</sup></b> (for patients ≤ 65y)****	IV	Ordered as <b>3000 mg/m<sup>2</sup></b> in exactly <b>500 mL</b> sodium chloride 0.9% <ul style="list-style-type: none"> <li>▪ <b>First dose</b> of MTX (<b>300 mg/m<sup>2</sup></b>): Administer <b>50 mL over 1 hour</b></li> <li>▪ <b>Second dose</b> of MTX (commence <b>immediately after the first dose</b>): (<b>2700 mg/m<sup>2</sup></b>): Administer <b>450 mL over 23 hours</b></li> </ul> <b>Total MTX infusion time: 24 hours</b>
			<b>2700 mg/m<sup>2</sup></b> (for patients ≤ 65y)****	IV	
11	+24	Hydration & urine alkalinization post-Methotrexate			See Table 1, page 4
12	+36	Calcium folinate (folinic acid) post-Methotrexate			See Table 1, page 4
15	0	<b>METHOTREXATE</b>	<b>12.5 mg</b>	IT	<b>INTRATHECAL</b> injection
16	+24	Calcium folinate (Folinic acid)	15 mg	PO	Single oral dose 24 hours post IT MTX
CYCLE FREQUENCY: 21–28 days, depending on counts recovery (see DOSE MODIFICATIONS).					

\* Dexamethasone is given as both pre-medication pre-Rituximab and anti-emetic. Note Dexamethasone 12 mg PO/IV = 12 mg sodium phosphate injection = 9.9 mg base injection [3 mL x 3.3 mg/mL]

\*\* 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 the first dose is well tolerated, consider rapid infusion rate from cycle 2 onwards.

\*\*\* **Patients > 70 years:** Maximum Vincristine dose is 1 mg.

\*\*\*\* **Patients > 65 years:** Starting intravenous MTX dose should be reduced to **1000 mg/m<sup>2</sup>** total dose in exactly **500 mL sodium chloride 0.9%** over 24 hours, administered as **100 mg/m<sup>2</sup> (50 mL)** over 1 hour, followed by **900 mg/m<sup>2</sup> (450 mL)** over 23 hours.

CNS disease: additional Intrathecal doses in <b>CYCLE 1 (first R-CODOX-M) only</b>					
Day(s)	Time [hrs]	Drug	Dose	Route	Administration details
6		<b>CYTARABINE</b>	<b>70 mg</b>	IT	<b>INTRATHECAL</b> injection
17	0	<b>METHOTREXATE (MTX)</b>	<b>12.5 mg</b>	IT	<b>INTRATHECAL</b> injection
18	+24	Calcium folinate (Folinic acid)	15 mg	PO	Single oral dose 24 hours post IT MTX

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

<p><b>Pre-hydration and urine alkalinization</b></p>	<ul style="list-style-type: none"> <li>▪ <b>Start 12 hours before methotrexate (MTX) infusion.</b></li> <li>▪ <b>IV</b> continuous infusion: 1000 mL Glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and <b>sodium bicarbonate 100 mmol</b>. Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6 m<sup>2</sup>). Duration: continuous infusion for 36 hours (run concurrently with the MTX infusion). <b>PO</b>: Sodium bicarbonate 1500 mg four times daily + 1500 mg 2-hourly when required.</li> <li>▪ Dipstick urine every 2 hours to check if pH ≥ 7. If pH under 7, give additional sodium bicarbonate (PO) 1500 mg.</li> </ul>												
<p><b>Urine output</b></p>	<ul style="list-style-type: none"> <li>▪ <b>Check every 4 hours.</b> Aim: 400 mL / m<sup>2</sup> / 4 hours (approximately 700 mL over 4 hours). Furosemide: Administer 20-40 mg to maintain urine output.</li> </ul>												
<p><b>Post-hydration and urine alkalinization</b></p>	<ul style="list-style-type: none"> <li>▪ <b>Start immediately at the end of MTX infusion.</b></li> <li>▪ <b>IV</b> continuous infusion: 1000 mL Glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and <b>sodium bicarbonate 50 mmol</b>. Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6 m<sup>2</sup>). Duration: continuous infusion until MTX level &lt; 0.1 µmol/L. <b>PO</b>: Sodium bicarbonate 1500 mg four times daily + 1500 mg 2-hourly when required.</li> <li>▪ Dipstick urine every 2 hours to check if pH ≥ 7. If pH under 7, give additional sodium bicarbonate (PO) 1500 mg.</li> <li>▪ Review the need for regular sodium bicarbonate at the end of MTX infusion and continue as appropriate until MTX levels &lt; 0.1 µmol/L.</li> </ul>												
<p><b>Calcium folinate (Folinic acid)</b></p>	<ul style="list-style-type: none"> <li>▪ <b>Start 36 hours after the start of MTX infusion: 15 mg/m<sup>2</sup> IV every 3 hours for 5 doses, then 15 mg/m<sup>2</sup> IV/PO* every 6 hours until MTX levels &lt; 0.1 µmol/L.</b></li> <li>▪ Based on plasma MTX levels and after discussing with the Consultant, calcium folinate dose may need adjustment as below.</li> </ul> <table border="1" data-bbox="384 1048 1417 1243"> <thead> <tr> <th colspan="4"><b>Calcium folinate (Folinic acid) dose adjustments according to plasma MTX levels after 48 hours from the start of MTX infusion</b></th> </tr> <tr> <th><b>Plasma MTX level</b></th> <th><b>&lt; 0.5 µmol/L</b></th> <th><b>0.5–1 µmol/L</b></th> <th><b>&gt; 1 µmol/L</b></th> </tr> </thead> <tbody> <tr> <td><b>Calcium folinate dose</b></td> <td><b>15 mg/m<sup>2</sup> IV/PO* every 6 hours</b></td> <td><b>50 mg/m<sup>2</sup> IV every 6 hours</b></td> <td><b>100 mg/m<sup>2</sup> IV every 6 hours</b></td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>* <b>PO tablets may only be given if the patient is not nauseous/vomiting and dose is ≤ 30mg as the tablet bioavailability greatly decreases with the higher doses.</b></li> <li>▪ Calcium folinate <b>100 mg/m<sup>2</sup> IV</b> 6 hourly should also be administered in patients with toxic plasma MTX levels after 36 hours from the start of MTX, or until MTX level is known following MTX overdose, or patients with clinical features of MTX toxicity (e.g. mucositis, signs of bone marrow suppression, hepatotoxicity or renal dysfunction).</li> <li>▪ Due to the large quantities of calcium, the infusion time of calcium folinate at doses &gt; 200–500 mg (or the patient's body surface area (BSA) × 50) should be over 1–2 hours. Monitor calcium concentrations closely.</li> </ul>	<b>Calcium folinate (Folinic acid) dose adjustments according to plasma MTX levels after 48 hours from the start of MTX infusion</b>				<b>Plasma MTX level</b>	<b>&lt; 0.5 µmol/L</b>	<b>0.5–1 µmol/L</b>	<b>&gt; 1 µmol/L</b>	<b>Calcium folinate dose</b>	<b>15 mg/m<sup>2</sup> IV/PO* every 6 hours</b>	<b>50 mg/m<sup>2</sup> IV every 6 hours</b>	<b>100 mg/m<sup>2</sup> IV every 6 hours</b>
<b>Calcium folinate (Folinic acid) dose adjustments according to plasma MTX levels after 48 hours from the start of MTX infusion</b>													
<b>Plasma MTX level</b>	<b>&lt; 0.5 µmol/L</b>	<b>0.5–1 µmol/L</b>	<b>&gt; 1 µmol/L</b>										
<b>Calcium folinate dose</b>	<b>15 mg/m<sup>2</sup> IV/PO* every 6 hours</b>	<b>50 mg/m<sup>2</sup> IV every 6 hours</b>	<b>100 mg/m<sup>2</sup> IV every 6 hours</b>										
<p><b>Glucarpidase</b></p>	<ul style="list-style-type: none"> <li>▪ <b>Consider early Glucarpidase</b> in MTX induced <b>renal dysfunction</b> (serum creatinine &gt; 1.5 x baseline and rising, or the presence of oliguria) and presence of <b>toxic plasma MTX levels</b>, which might be life-threatening despite rescue measures: <b>&gt; 30 µmol/L after 36 hours, &gt; 10 µmol/L after 42 hours, or &gt; 5 µmol/L after 48 hours from the start of MTX infusion.</b></li> <li>▪ 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.</li> <li>▪ The recommended dose is one single intravenous injection of <b>50 units/kg</b>. Multiple doses are not permitted. <b>Blueteq</b> is required. Refer to <a href="#">[NHSE Glucarpidase policy]</a> and <a href="#">[TVCA Glucarpidase guideline]</a> for more details.</li> </ul>												

R-IVAC					
High-risk disease: CYCLES 2 and 4 (alternating with R-CODOX-M)					
Day(s)	Time [hrs]	Drug	Dose	Route	Administration details
1		Paracetamol Dexamethasone* Chlorphenamine	1000 mg 12 mg 10 mg	PO PO/IV IV	≥ 30 minutes before Rituximab
1		<b>RITUXIMAB</b>	<b>375 mg/m<sup>2</sup></b>	<b>IV</b>	In 500 mL sodium chloride 0.9%**
1–5		<b>ETOPOSIDE</b>	<b>60 mg/m<sup>2</sup></b>	<b>IV</b>	in 500 mL of sodium chloride 0.9% over 1 hour
1–5	-15-30 min.	Mesna Pre-Ifosfamide	300mg/m <sup>2</sup> (for patients ≤ 65y)****	IV	in 50-100 mL sodium chloride 0.9% over 15-30 minutes
1–5	0	<b>IFOSFAMIDE &amp; MESNA</b>	<b>1500 mg/m<sup>2</sup> &amp; 1500 mg/m<sup>2</sup></b> (for patients ≤ 65y)****	<b>IV</b>	in 1000 mL sodium chloride 0.9% over 1 hour
1–5	+4, +8	Mesna Post-Ifosfamide	450mg/m <sup>2</sup> TWICE daily (for patients ≤ 65y)****	IV***	Administer at 4 hours and 8 hours after the START of Ifosfamide infusion: in 50-100 mL sodium chloride 0.9% over 15-30 minutes
1–2		<b>CYTARABINE</b>	<b>2000 mg/m<sup>2</sup> TWICE daily</b> (for patients ≤ 65y)****	<b>IV</b>	in 500 mL of sodium chloride 0.9% over 3 hours <b>For outpatients:</b> via an ambulatory infusion pump. If the maximum flow rate of infusion pump is > 125 mL/hour, replace diluent with 100 mL sodium chloride 0.9%.
5	0	<b>METHOTREXATE</b>	<b>12.5 mg</b>	<b>IT</b>	<b>INTRATHECAL</b> injection
6	+24	Calcium folinate (folinic acid)	15 mg	PO	Single oral dose 24 hours post IT Methotrexate
CYCLE FREQUENCY: 21–28 days, depending on counts recovery (see DOSE MODIFICATIONS).					

\* Dexamethasone is given as both pre-medication pre-rituximab and anti-emetic. Note Dexamethasone 12 mg PO/IV = 12 mg sodium phosphate injection = 9.9 mg base injection [3 mL x 3.3 mg/mL]

\*\* 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 the first dose is well tolerated, consider rapid infusion rate from cycle 2 onwards.

\*\*\* **For patients with good oral intake**, consider replacing post-Ifosfamide Mesna intravenous infusion with **oral Mesna 900mg/m<sup>2</sup> PO given at 2 hours and 6 hours** after the END of ifosfamide infusion.

\*\*\*\* **Patients > 65 years:** Starting dose of Ifosfamide & Mesna, as well as Cytarabine should be reduced as follows:

- Mesna pre-Ifosfamide: 200 mg/m<sup>2</sup>
- **Ifosfamide & Mesna: 1000 mg/m<sup>2</sup> & 1000 mg/m<sup>2</sup>**
- Mesna post-Ifosfamide: IV: 300 mg/m<sup>2</sup> x 2 doses, OR PO: 600 mg/m<sup>2</sup> x 2 doses
- **Cytarabine: 1000 mg/m<sup>2</sup> TWICE daily**

CNS DISEASE: additional Intrathecal doses in CYCLE 2 (first R-IVAC) only					
Day(s)	Time [hrs]	Drug	Dose	Route	Administration details
7, 9		<b>CYTARABINE</b>	<b>70 mg</b>	<b>IT</b>	<b>INTRATHECAL</b> injection

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## CONCURRENT MEDICATIONS

Cycle 1 only (first R-CODOX-M)	
<b>TLS prophylaxis</b>	Hydration + allopurinol 300mg OD (reduce dose in renal impairment) for 7 days, or consider rasburicase if high risk TLS [Cycle 1]. Refer for full details to the Tumour Lysis Syndrome in Adults protocol <a href="#">[H.8]</a> .

All Cycles of R-CDOX-M and R-IVAC	
<b>Antiviral prophylaxis</b>	Aciclovir 200mg TDS during treatment and for 3 months after completion
<b>Antifungal prophylaxis</b>	Fluconazole 50 mg OD for duration of treatment
<b>PJP prophylaxis</b>	Pentamidine 4mg/kg IV infusion once a month (max. 300mg) until the end of last cycle. Once MTX level is < 0.1 micromol/L after the last MTX dose, start Co-trimoxazole 480mg three times a week on Mon/Wed/Fri for at least 3 months. Note: Avoid Co-trimoxazole during MTX treatment and until the end of last cycle due to interaction with MTX – see INTERACTIONS below.
<b>Gastric protection</b>	Famotidine 20mg BD during treatment and until platelets > 50 x 10 <sup>9</sup> /L, unless otherwise indicated [avoid PPIs – see INTERACTIONS below]
<b>Mouth care/mucositis</b>	Benzydamine 0.15% mouthwash 15 mL as mouthwash QDS when required
<b>Menstrual bleeding prevention*</b>	If required: Norethisterone 5-10mg TDS for duration of treatment and until platelets count > 50 x 10 <sup>9</sup> /L, unless otherwise indicated
<b>Vitamin D supplement*</b>	If required: Vitamin D < 50 nmol/L: replace as per local formulary

(\*) indicates optional concurrent medications

R-CODOX-M specific supportive medications	
<b>Hydration and urine alkalinization pre- &amp; post-MTX / Calcium folinate – see Table 1, page 4.</b>	
<b>Anti-emetics</b> Day 1: High risk Days 2-5 & 10: Moderate risk Day 8: Minimal	<ul style="list-style-type: none"> <li>▪ Dexamethasone on day 1: 12mg OM (pre-medication prior to Rituximab) &amp; days 2–5: 8mg OM</li> <li>▪ Ondansetron on days 1-5 &amp; 10: 8mg BD</li> <li>▪ Metoclopramide on days 1–8 &amp; 10-14: 10-20mg TDS. For breakthrough nausea or vomiting: 10-20mg TDS when required.</li> </ul> For alternative options, refer to <a href="#">[TVCA Anti-emetic guideline]</a> .
<b>G-CSF</b>	Filgrastim <b>0.5 MU/kg/day</b> , starting <b>from day 13</b> for 7 days or longer if needed until neutrophils > 1.0 x 10 <sup>9</sup> /L

R-IVAC specific supportive medications	
<b>Hemorrhagic cystitis prophylaxis</b>	<b>Mesna</b> – see DRUG REGIMEN above. For management of positive urine dips for blood, follow treatment dosing in DOSE MODIFICATIONS below.
<b>Cytarabine-induced conjunctivitis prophylaxis</b>	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 1 of high dose Cytarabine 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.
<b>Anti-emetics</b> Days 1-2: High risk Days 3-5: Moderate risk	<ul style="list-style-type: none"> <li>▪ Dexamethasone on day 1: 12mg OM (pre-medication prior to Rituximab) &amp; days 2–5: 8mg OM</li> <li>▪ Ondansetron on days 1-5: 8mg BD</li> <li>▪ Metoclopramide on days 1–8: 10-20mg TDS. For breakthrough nausea or vomiting: 10-20mg TDS when required.</li> </ul> For alternative options, refer to <a href="#">[TVCA Anti-emetic guideline]</a> .
<b>G-CSF</b>	Filgrastim <b>0.5 MU/kg/day</b> , starting <b>from day 7</b> for 7 days or longer if needed until neutrophils > 1.0 x 10 <sup>9</sup> /L

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## CONTRAINDICATIONS

Hypersensitivity to active ingredients and excipients. Active severe infections. Refer for full details to individual medications Summary of Product Characteristics (SmPCs).

## INVESTIGATIONS

- Before each cycle: FBC, U&Es, creatinine, calcium, magnesium, LFTs, urate, glucose
- Daily plasma **MTX levels, starting from 36 hours after the start of MTX infusion, then at 42 and 48 hours, and subsequently every 24 hours.** Blood samples taken out of hours at 36 and 42 hours can be sent to the laboratory as soon as possible within working hours. All samples must be clearly labelled with the time points of when the levels were taken to ensure correct interpretation of results.
- When clinically indicated: neurological examination, ECG.

## RESTAGING

At the completion of treatment: low risk disease after 3 cycles and for high-risk disease after 4 cycles. Can consider interim scan after 2 cycles for high-risk disease.

## TREATMENT MODIFICATIONS

**All dose modifications should be discussed with the Consultant.**

<p><b>Haematological toxicities</b></p> <p>There are no dose modifications for haematological toxicities. However, the start of the cycle will depend on the counts' recovery:</p> <ul style="list-style-type: none"> <li>▪ If ANC &gt; 1.0 x 10<sup>9</sup>/L and platelets &gt; 75 x 10<sup>9</sup>/L, stop the G-CSF. If counts are maintained after 24 hours, commence next cycle of chemotherapy.</li> <li>▪ If ANC &gt; 1.0 x 10<sup>9</sup>/L but platelets are &lt; 75 x 10<sup>9</sup>/L, stop G-CSF and await platelet recovery.</li> <li>▪ Platelets &lt; 40 x 10<sup>9</sup>/L: Consider delay of the <b>intrathecal</b> treatment if the platelet count is very low or coagulation is abnormal. If platelets &lt; 40 x 10<sup>9</sup>/L give 1-2 pools of platelets (depending on prior platelet increments) just before procedure. Correct any coagulation abnormality as clinically indicated.</li> </ul>
<p><b>Non-haematological toxicities</b></p> <p><b>Grade 3 or 4:</b> Next cycle should be delayed until toxicity grade is ≤ 2.</p>
<p><b>Doxorubicin-induced Cardiotoxicity</b></p> <ul style="list-style-type: none"> <li>▪ Consider doxorubicin cardiotoxicity and maximum lifetime anthracycline exposure. Doxorubicin must be used with caution, if at all, in patients with cardiac dysfunction – discuss with the Consultant.</li> <li>▪ <b>Recommended total maximum cumulative dose of doxorubicin</b> (additive to other anthracyclines): 450 mg/m<sup>2</sup> (in normal cardiac function) or 400 mg/m<sup>2</sup> (in cardiac dysfunction, age &gt; 70 years or exposure to mediastinal irradiation).</li> </ul>
<p><b>Vincristine-induced Neuropathy</b></p> <ul style="list-style-type: none"> <li>▪ In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding Vincristine with the Consultant.</li> </ul>
<p><b>Cyclophosphamide-induced Haemorrhagic cystitis</b></p> <ul style="list-style-type: none"> <li>▪ If gross hematuria develops, Cyclophosphamide should be withheld until resolution of cystitis and Mesna treatment commenced as per SmPC.</li> <li>▪ Cyclophosphamide dose reduction by 50% may be considered at the next cycle. Re-escalation of cyclophosphamide to the initial full dose is recommended if symptoms do not recur.</li> </ul>
<p><b>Tumour lysis syndrome (TLS) Grade 3 or 4</b></p> <p>Following complete resolution of TLS, treatment may be restarted at the full/current doses during the next scheduled cycle in conjunction with prophylactic therapy.</p>

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### Ifosfamide-induced Haemorrhagic cystitis: Managing positive urine dip for blood

Refer to [\[TVCA Guideline for Managing Positive Blood on Urine dips for Inpatients on Ifosfamide\]](#)

Test Result	Action
Trace	Re-test
+	Re-test; if positive on more than one consecutive test give additional IV bolus Mesna. Check fluids and any concurrent Mesna is running correctly.
++ / +++	Double dose of any concurrently running IV Mesna until haematuria resolved. Continue the separate Mesna infusion until the patient is reviewed and for 24 hours after the Ifosfamide infusion has finished. Repeated ++ / +++ result, or evidence of macroscopic haematuria should prompt pause and review of current treatment.

**Recommended Mesna dose:** 600mg/m<sup>2</sup> intravenous bolus or a fixed dose of 1 gram in 250 mL sodium chloride 0.9% infusion over 30 minutes. Patients needing bolus Mesna should have their infusional Mesna doubled for all subsequent chemotherapy treatments. **Ambulatory patients should be carefully risk assessed for admission in future cycles.**

### Ifosfamide-induced Encephalopathy

Refer to **Appendix 1** to assess risk.

Symptoms <sup>§</sup>	Intervention
<b>Mild (Grade 1)</b> somnia, agitation, tremor, delirium or extrapyramidal symptoms	<ul style="list-style-type: none"> <li>Monitor neurological status (standard neurological observations).</li> <li><b>Limit rate</b> of Ifosfamide infusion, <b>maximum rate 1 g/m<sup>2</sup>/hour.</b></li> </ul>
<b>Moderate (Grade 2)</b> somnia, agitation, tremor, delirium or extrapyramidal symptoms	<ul style="list-style-type: none"> <li>Strict monitoring of neurological status every 30 minutes.</li> <li><b>Limit rate</b> of Ifosfamide infusion, <b>maximum rate 1 g/m<sup>2</sup>/hour.</b></li> <li><b>Start Methylthionium chloride (Methylene blue) 50 mg* IV 4 hourly</b> - continue treatment until all signs of neurotoxicity have resolved.</li> <li><b>If worsening toxicity, STOP Ifosfamide, continue Mesna.</b></li> <li><b>Consider prophylactic Methylthionium chloride (Methylene blue) with the next cycle.</b></li> </ul>
<b>Severe (Grade 3 and 4)</b> somnia, agitation, tremor, delirium or extrapyramidal symptoms <b>OR any other severe neurological event</b> e.g., toxic psychosis, seizures, coma	<ul style="list-style-type: none"> <li>Strict continuous monitoring of neurological status. Consider ICU review.</li> <li><b>Immediately STOP Ifosfamide, continue Mesna.</b></li> <li><b>Start Methylthionium chloride (Methylene blue) 50 mg* IV 4 hourly</b> - continue treatment until all signs of neurotoxicity have resolved.</li> <li><b>Avoid further treatment with Ifosfamide.</b></li> </ul>

<sup>§</sup>Grading as per CTCAE 5.0, list of possible symptoms is not exhaustive.

<b>Methylthionium chloride (Methylene blue)</b>	<p><b>*Dosage:</b> In patients weighing significantly below 50 kg, Methylthionium chloride (Methylene blue) can be dosed at 1 mg/kg (up to a maximum single dose of 50 mg) 4 or 6-hourly rounded to the nearest 5 mg dose. In most cases, symptoms resolve within 48–72 hours of ifosfamide discontinuation (Lee Brink, 2020).</p> <p><b>Prophylactic dose: 50 mg IV 8 hourly</b>, started on the first day of Ifosfamide infusion and continued for 24 hours after the last dose.</p> <p><b>Administration:</b> Dilute Methylthionium chloride 50 mg in 50 mL glucose 5%. Give as IV infusion over 15–30 minutes. If available, deliver through a central venous device (due to low pH of 3–4.5). Flush with glucose 5%.</p> <p><b>Precautions:</b> Due to the potential risk of cardiac arrhythmia and hypotension, electrocardiograph (ECG) and blood pressure monitoring are recommended.</p> <p><b>Vesicant (extreme low pH).</b> In the case of extravasation, refer to local extravasation policy.</p> <p><b>Contraindications include G6PD deficiency (refer to the SmPC for the full list).</b></p>
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Renal impairment	
<b>Doxorubicin</b>	GFR ≥ 10 mL/min: 100% dose GFR < 10 mL/min: no need for dose adjustment is expected
<b>Vincristine</b>	No need for dose adjustment is expected
<b>Cyclophosphamide</b>	GFR ≥ 30 mL/min: 100% dose GFR 10-29 mL/min: 75% dose GFR < 10 mL/min: omit or consider 50% dose at the Consultant discretion
<b>Methotrexate</b>	GFR ≥ 80mL/min: 100% dose GFR 50-79: 100% dose or consider dose reduction at the Consultant discretion* GFR < 50mL/min: omit
<b>Etoposide</b>	GFR ≥ 50mL/min: 100% dose GFR 15-49mL/min: 75% dose GFR < 15mL/min: Clinical decision. Further dose reduction usually required, consider overall regimen feasibility.
<b>Ifosfamide</b>	GFR ≥ 60mL/min: 100% dose GFR 40-59mL/min: 70% dose GFR < 40mL/min: Clinical decision, discuss with the Consultant. Cyclophosphamide may be considered as an alternative.
<b>Cytarabine</b>	GFR ≥ 60 mL/min: 100% dose GFR 31-59 mL/min: 50% dose GFR ≤ 30 mL/min: omit

\* Discuss with the 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.

Hepatic impairment	
<b>Doxorubicin</b>	Bilirubin < 20 µmol/L: 100% dose Bilirubin 20–50 µmol/L: 50% dose Bilirubin 51–86 µmol/L: 25% dose Bilirubin or Child-Pugh C > 86 µmol/L: omit
<b>Vincristine</b>	Bilirubin > 51 µmol/l: 50% dose
<b>Cyclophosphamide</b>	Mild and moderate: no need for dose adjustment is expected Severe: not recommended due to risk of reduced efficacy
<b>Methotrexate</b>	Mild and moderate: caution required, consider dose reduction or discontinue with concomitant renal impairment or constant increase in liver enzymes (see below**) – clinical decision. Severe: avoid use.
<b>Etoposide</b>	Bilirubin < 50 umol/L, AND normal albumin AND normal renal function: 100% dose Bilirubin ≥ 50 umol/L <b>OR</b> decreased albumin levels: Consider 50% dose, increase if tolerated well. * Patients with raised bilirubin and/or decreased albumin may have an increase in free etoposide and hence greater myelosuppression.
<b>Ifosfamide</b>	Mild or Moderate (Child Pugh A or B): no need for dose adjustment is expected. Severe (Child Pugh C): Not recommended. ** Ifosfamide is protein bound, therefore patients presenting with a significant hypoalbuminemia may be at greater risk of neurotoxicity. Careful assessment of the neurotoxicity risk is recommended (see <b>Appendix 1</b> ).
<b>Cytarabine</b>	Mild and Moderate: no need for dose adjustment is expected. Severe: consider 25-50% of the original dose and increase if tolerated.

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

**DRUG INTERACTIONS**

CYP3A4 and P-gp inhibitors	Increased risk of doxorubicin, vincristine and cyclophosphamide toxicities; when used concurrently, use with caution and monitor closely. Although not studied, fluconazole may increase the plasma levels of vincristine and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4. Can be used concurrently with caution and patient monitored closely for vincristine side-effects.
CYP3A4 inducers	Doxorubicin, vincristine and cyclophosphamide efficacy can be decreased; when used concurrently, use with caution and monitor closely.
Rituximab	Since hypotension may occur during rituximab administration, consider withholding anti-hypertensive medication(s) 12 hours prior to rituximab infusion.
Dexamethasone	Dexamethasone may increase blood glucose levels. Insulin and/or oral hypoglycemic agents may require dosage adjustments.
Methotrexate	<ul style="list-style-type: none"> <li>▪ 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 &lt; 0.1 micromol/L after last cycle.</li> <li>▪ Penicillins: avoid concomitant use. Reduced renal clearance of methotrexate can occur. Tazocin (piperacillin with tazobactam) should NOT be used until MTX levels &lt; 0.1 micromol/L – use alternative as per local formulary and antibiotic guidelines.</li> <li>▪ 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).</li> <li>▪ PPI: avoid concomitant use. Delayed elimination &amp; increased serum MTX can occur.</li> </ul>
Etoposide	<ul style="list-style-type: none"> <li>▪ Consider potential for increased toxicity (with CYP3A4 inhibitors) and decreased efficacy (with CYP3A4 inducers) of etoposide.</li> <li>▪ Co-administration with antiepileptics can lead to decreased seizure control.</li> <li>▪ Co-administration of warfarin and etoposide may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.</li> </ul>
Ifosfamide	Ifosfamide possibly enhances effect of warfarin (may increase INR)
Cytarabine	Cytarabine may reduce plasma digoxin levels – consider monitoring. It can also antagonise the activity of gentamicin against Klebsiella pneumoniae (based on one in vitro study), in which case, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.
Intrathecal injections	Anticoagulants and antiplatelets can increase the risk of bleeding when intrathecal MTX is administered during the lumbar puncture. Consider the risk of bleeding vs risk of thrombosis when suspending anticoagulants and antiplatelets. Refer to the <a href="#">[BMJ Neurology Guideline]</a> and summary of recommendations in <b>Table 2</b> below.

**Table 2. Recommendations for discontinuation of medications in patients with normal renal function (creatinine clearance ≥ 50 mL/min).**

	Anticoagulants					Antiplatelets	
	LMWH prophylaxis	LMWV treatment	Rivaroxaban + Apixaban	Dabigatran	Warfarin	Aspirin 75mg	Clopidogrel
<b>Withhold before IT MTX</b>	12 hours	24 hours	24 hours	48 hours	5 days* check INR ≤ 1.4	continue	7 days (Consider aspirin)
<b>First dose after IT MTX</b>	4 hours	4 hours (24 hrs if traumatic)	6 hours	6 hours	12 hours	No delay	6 hours

\*Warfarin – consider bridging with LMWH in high-risk patients.

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## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- Neutropenia and febrile neutropenia – primary prophylaxis with G-CSF is recommended.
  - Alopecia
  - Nausea and vomiting – prophylaxis with anti-emetics is recommended.
  - **Cyclophosphamide and ifosfamide** may irritate the bladder mucosa. Patients should be encouraged to drink a minimum of three litres of fluid per 24 hours.
  - **Doxorubicin** may cause cardiotoxicity. Monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity, e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
  - **Vincristine** may cause neurotoxicity. It is for intravenous use only; fatal if given by other routes.
  - **Rituximab** may cause patient chilliness, 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), mucositis, stomatitis, diarrhoea, skin changes and increased skin sensitivity to sun, gritty eyes, hair loss, neurotoxicity including headache, dizziness, blurred vision and loss of balance.
- Photosensitivity reactions** – [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].
- **Etoposide:** alopecia, appetite decreased, arrhythmia, constipation, bone marrow suppression, hepatotoxicity, mucositis, diarrhoea, nausea, vomiting.
  - **Ifosfamide:** neurotoxicity, encephalopathy, nephrotoxicity, hypokalaemia, hypocalcaemia, hypophosphataemia, alopecia, nausea, vomiting, decreased appetite. haemorrhagic cystitis.
  - **Cytarabine:** nausea, diarrhoea, oral ulceration, hepatic dysfunction, neuropathy, pulmonary toxicities, cardiomyopathy, ocular toxicities; reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia. “**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 cytarabine administration. Cerebellar toxicity is also a recognised, albeit rare, side effect of high dose cytarabine.
  - **Steroid-related** side effects may include osteoporosis, hyperglycaemia, hypertension, eye disorders, hypokalaemia, susceptibility to infection, gastrointestinal side-effects (peptic ulceration, indigestion), thinning of the skin. Monitor BMs, BP, electrolytes. Use with caution in patients with co-morbidities (including diabetes, cardiovascular diseases, glaucoma).
  - **Lumbar puncture side-effects:** Most common: headache, swelling, bruising or discomfort in lower back. Less common: arachnoiditis; fever, infection, rarely leucoencephalopathy. Intrathecal methotrexate and cytarabine will reach the blood stream and can have systemic effects.

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## EXTRAVASATION RISK

Cyclophosphamide: neutral  
 Cytarabine: neutral  
 Doxorubicin: vesicant  
 Etoposide: irritant  
 Ifosfamide: neutral  
 Methotrexate: inflammatory agent  
 Vincristine: vesicant  
 Rituximab: neutral

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## TREATMENT RELATED MORTALITY

5%

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## REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Cheung, Pharmacist	Addition of oral as alternatives to IV MESNA during IVAC cycles.	Sep 2018	4.3	May 2020
NSSG Lymphoma Group	Annual protocol review	Aug 2020	4.4	May 2021
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist, NSSG Lymphoma & CLL Group	Pre-assessment [glycaemic control; MHRA advice on MTX photosensitivity reactions added]. Drug regimen updated [Mesna, Cytarabine, MTX hydration and toxicity prophylaxis & management]. Concurrent medications, contraindications, MTX dose modifications (renal impairment), interactions, adverse reactions, references updated. Ambulatory care information and Appendix 1 added. General formatting. Annual protocol review.	September 2024	5.0	September 2026

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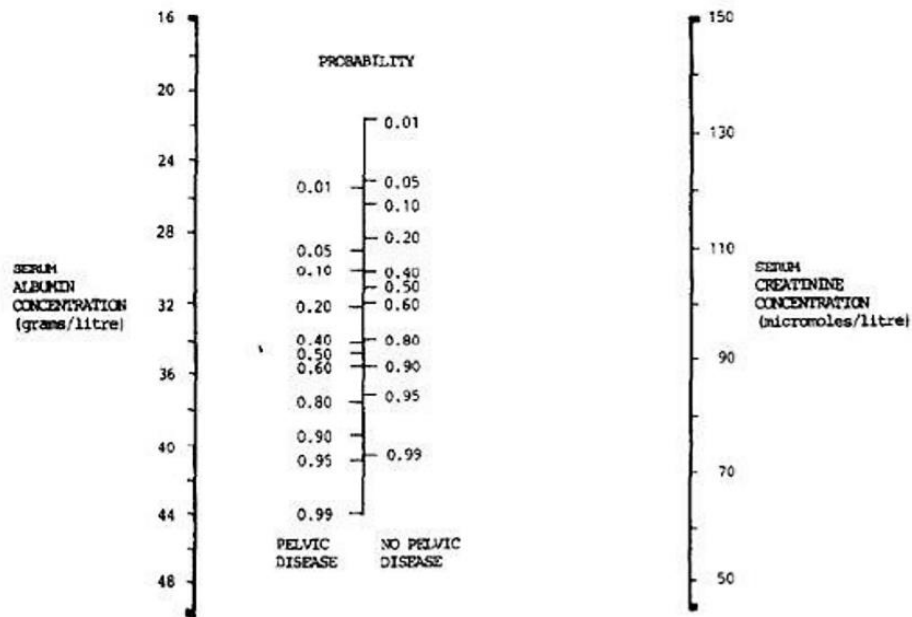
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**Appendix 1. Ifosfamide neural toxicity nomogram.**

The following nomogram can be used, to aid decision making, regarding the use of prophylactic methylene blue. Pre-treatment albumin and creatinine should be measured, and a ruler placed across the two values. Use the relevant scale depending on the presence of pelvic disease.

Consider:

- Previous Ifosfamide induced neurotoxicity
- Serum creatinine > 150 µmol/L
- Serum albumin < 30 g/L



*Fig. 1. Nomogram to determine probability of not developing grade 3–4 clinical CNS toxicity with ifosfamide/mesna 36 hr infusion. The probability that a patient will **NOT** develop severe CNS toxicity falls on the intersection of a straight line joining their serum albumin and serum creatinine concentrations on the appropriate pelvic disease scale.*

Reference: Meanwell, C., Blake, A., Kelly, K., Honigsberger, L. and Blackledge, G. (1986). Prediction of Ifosfamide/Mesna associated encephalopathy. Eur J Cancer Clin Oncol 22 (7), pp. 815-819.

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