Nottingham University Hospitals NHS Trust

USE OF HIGH DOSE METHOTREXATE AND FOLINIC ACID RESCUE

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Explicit definition of patient group to which it applies *(e.g. inclusion and exclusion criteria, diagnosis):*	Clinical haematology patients who require high dose methotrexate
Changes from previous version *(not applicable if this is a new guideline, enter below if extensive):*	Updated front sheet, new SOP for nursing staff

Summary of evidence base this guideline has been created from:	These policies have been compiled over the past few years in line with evidence for best practice reviewed in the literature from other centres managing patients with similar conditions. The aim is to treat patients with haematological malignancies safely, minimising the risks to the patients and staff from the treatments given.
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.	

GUIDELINE FOR THE USE OF HIGH DOSE METHOTREXATE AND FOLINIC ACID RESCUE

METHOTREXATE SCHEDULES

Please note that there are two schedules for high-dose intravenous Methotrexate (MTX) that differ in their infusion times (3 hours versus 24 hours), dose (3.5g/m^2 versus 3g/m^2), timing of folinic acid rescue (24 hours versus 36 hours) and folinic-acid dose-adjustment protocol. Critical aspects as below will be highlighted in red throughout the protocol.

Please ensure that you refer to the correct section of the protocol, appropriate for the Methotrexate schedule that a particular patient is receiving.

Schedule 1 is the 24 hour infusion, typically used in Acute Lymphoblastic Leukaemia (ALL) protocols either as a single-agent or as part of a multi-agent regimen.

Schedule 2 is the 3 hour infusion, predominantly used for the **treatment** or prophylaxis of central nervous system lymphoma (CNSL). This can be administered either as a single-agent; typically for CNS prophylaxis in selected patients with high-grade NHL, or in combination (e.g. MATRix, RMA, RMP); typically for patients with primary or secondary CNS lymphoma. This is also employed within the multi- agent Burkitt/DLCBL regimen: R-CODOX-M/R-IVAC.

General Considerations

1. Baseline bloods prior to administration of High-Dose Methotrexate

This relates to both schedules, the details of which are outlined separately below

Prior to each MTX infusion and within 48 hours of administration, measure:

- U+E (urea, creatinine and electrolytes)
- LFT (Bilirubin, ALT, albumin)
- FBC

Prior to each MTX infusion, determine Creatinine Clearance (CrCl-Cockcroft-Gault calculation is sufficient for most patients). Meticulous attention should be paid at all times to the Creatinine Clearance. The initial Creatinine Clearance before starting MTX should ideally be over 70ml/min, consider dose modification if CrCl < 70ml/min. Dose reductions are usually required if the CrCl is less than 50 mls/min (see below).

2. Dose reduction of Methotrexate according to Creatinine Clearance

For both schedules (3g/m^2 and 3.5g/m^2) dosing of MTX is influenced by CrCl. Dose reductions are usually undertaken as follows:

CrCl (ml/min)	Dose of MTX
>70	100%
50-69	75-100%*
30-49	50%**
<30	0

*Consider 25% dose reduction – discuss with Consultant
**Discuss with Consultant

Note that dose reductions of MTX **do not apply to the loading dose** (this should remain at full dose to address the distribution phase of MTX). Any dose reductions **do** apply to the second bag of MTX (i.e. the 2700mg/m^2 dose for schedule 1 and the 3000mg/m^2 dose for schedule 2)

For subsequent cycles of MTX, an up-to-date weight-based CrCl calculation should be performed, together with a review of any toxicities encountered and/or delays to methotrexate excretion, to inform dose reduction decisions (discuss with Consultant).

If a dose reduction of MTX is made for the first cycle based on CrCl but there is prompt excretion of methotrexate with no renal or systemic toxicity, a decision may be made to increase the dose for the next cycle. This should be a Consultant decision only, made on an individual patient basis.

IF A PATIENT IS PARTICIPATING IN A CLINICAL TRIAL PROTOCOL INCORPORATING HIGH-DOSE MTX, THE CURRENT VERSION OF THE TRIAL PROTOCOL MUST BE REFERRED TO; ALTERNATE FOLINIC ACID SCHEDULES MAY EXIST (E.G. UKALL 2011)

3. Clinical considerations

Third-space fluid (ascites, pleural effusions etc.) may cause resorption of MTX, delayed clearance and increased MTX toxicity – seek Consultant advice before proceeding if any of these is present.

Assess for evidence of sepsis or other potential co-factors that may increase risk of MTX toxicity (e.g. fever, systemic infection, hypotension). MTX administration should not proceed with an active infection unless approved by a Consultant.

4. Drug interactions

PATIENTS MUST NOT RECEIVE CO-TRIMOXAZOLE WITHIN 72 HOURS PRIOR TO THEIR METHOTREXATE INFUSION. DISCUSS WITH THE PATIENT'S CONSULTANT IF THE PATIENT HAS RECEIVED CO-TRIMOXAZOLE WITHIN 72 HOURS OF ADMISSION. Refer to Trial specific protocol where appropriate.

For those patients who are scheduled to have multiple MTX cycles, nebulised pentamidine (or oral atovaquone where nebulised pentamidine is not safe or likely not to be tolerated) may be more appropriate as prophylaxis against Pneumocystis jiroveci pneumonia.

Methotrexate is a potentially nephrotoxic drug so great care should be taken to avoid co-administration of any drugs that may compromise renal function and/or lead to impaired excretion of MTX. Such drugs should be avoided concurrent with, and 48 hours prior to start of MTX.

These include but are not limited to:

- Aminoglycosides (e.g. Gentamicin, Amikacin)
- NSAIDs
- Penicillins (eg Tazocin, Co-amoxiclav po or IV) may interfere with the active renal tubular secretion of MTX

MEROPENEM monotherapy is the antibiotic of choice if a patient receiving MTX requires treatment for febrile neutropenia prior to or during MTX infusion.

TAZOCIN and/or GENTAMICIN should NOT be used

Protocol for administration of Methotrexate

If clinically appropriate and the laboratory results are within normal limits, proceed with MTX

administration according to the following steps:

1. **Pre-hydration**

   This should be started at least 6 hours prior to the commencement of the intravenous MTX.

   Hydration fluid - 1 litre glucose 4% , saline 0.18%, potassium chloride 20mmol/L to which sodium bicarbonate has been added. Refer to ChemoCare prescription. Alternating bags of sodium chloride 0.9% and glucose 5% is acceptable.

   Infusion rate – Approximately 125 ml/m^2/hr. This rate may be modified whilst the MTX infusion is running, please refer to ChemoCare prescription.

   Check urine pH - Adjust the sodium bicarbonate concentration to maintain the urinary pH 8 and above (i.e. alkaline). A urinary pH of 8 or greater must be achieved before starting the MTX infusion.

2. **High-dose methotrexate infusion**

   TREATMENT SHOULD COMMENCE BETWEEN 0800HRS AND 01200HRS, UNLESS AUTHORISED BY A CONSULTANT. This ensures serum MTX LEVELS ARE APPROPRIATELY INTERPRETED.

   The particulars of administration will be covered below for each of the MTX schedules.

3. **Post-hydration and folinic acid rescue**

   Hydration fluid and urine pH monitoring should be continued during MTX administration and post-hydration period until the MTX serum levels have reached the desired value.

   Folinic acid rescue enhances clearance of serum MTX and is an integral part of the MTX regime. It should be started 24h after the start of the MTX infusion. Ensure this is included in the drug chart once the start time of MTX has been noted. Liaise with the nurse looking after the patient to obtain the exact time of start of MTX.

   Measurement of MTX level are dependent on the schedule utilised, please refer to the appropriate section below for more details.

   Monitoring MTX excretion

   Following HD-MTX administration, excretion of the drug is carefully monitored with serum levels that should start at a specific time-point depending on the protocol/schedule and will have to be continued until serum levels are appropriately cleared.

   The timing of measurement of serum MTX with respect to the time of initiation is critical for interpretation of results. As soon as the MTX infusion is started, request for serum MTX levels should be made to ensure the samples are taken at the correct time.

Laboratory parameters to be measured during folinic acid rescue:

Daily U+Es and MTX level

Alternate days Bilirubin, ALT, albumin, full blood count.

IF THE SERUM CREATININE INCREASES BY MORE THAN 25% from BASELINE THEN FOLINIC ACID RESCUE SHOULD BE ESCALATED EVEN BEFORE THE MTX LEVEL IS KNOWN – SEEK CONSULTANT ADVICE IF REQUIRED.

IF SEVERE MTX TOXICITY IS SUSPECTED THEN SEEK EARLY CONSULTANT ADVICE REGARDING THE USE OF RECOMBINANT GLUCARPIDASE/ CARBOXYPEPTIDASE AND REFER TO NHSE GUIDANCE, SEE APPENDIX 4

Schedule 1 (24 hour infusion): Methotrexate administration, monitoring and Folinic Acid rescue

METHOTREXATE INFUSIONS SHOULD COMMENCE BETWEEN 0800HRS AND 1200HRS (MIDDAY). CONSULTANT ADVICE SHOULD BE SOUGHT IF THE START TIME IS LIKELY TO BE AFTER 12:00HOURS. ALL SERUM MTX LEVELS SHOULD BE TAKEN AT 24 HOUR INTERVALS FROM THE DOCUMENTED START TIME OF MTX.

ALL TIMES ARE MEASURED FROM THE START OF THE METHOTREXATE INFUSION.

Methotrexate 3g/m^2 dose:

10% (i.e. 300 mg/m^2) given in first hour (loading dose).

90% (i.e. 2700 mg/m^2) given over next 23 hours.

NB: The infusion of MTX must always stop at 24 hours even if not completed for any reason.

Hydration continues during the methotrexate infusion at a modified rate, refer to ChemoCare prescription.

Dosage of folinic acid:

FOLINIC ACID RESCUE MUST START AT 36 HOURS FROM THE START OF METHOTREXATE

It must be written up at the time of prescribing the MTX infusion.

At 36 hours: Give **15 mg/m^2** iv.

36-48 hours: Give **15 mg/m^2** iv every 3 hours.

From 48 hours: Give **15 mg/m^2** iv every 6 hours until MTX level is less than **0.1 µmol/l**

(1.0x10^{-7} M). If the patient is not vomiting, folinic acid may be given orally after the first two doses.

Monitoring Of Plasma Methotrexate Levels Following Infusion.

Times given are from time 0 (time of starting intravenous MTX infusion).
The following plasma samples are **required for patient's safe rescue** with folinic acid:
48 hours, 72 hours, and then every 24 hours if not completely rescued, i.e. until plasma methotrexate level are less than **0.1 µmol/l (**1 x 10^{-7} M). Higher levels may be acceptable but only after discussion with Consultant

Adjustments to dose of folinic acid rescue

Delayed MTX excretion will require increase in the dose of Folinic Acid as below.

If the 48-hour (from start of MTX infusion) **methotrexate level is > 20µmol/l (2 x 10^{-5} M), INCREASE the dose of folinic acid iv as below.**

If the 72-hour (from start of MTX infusion) **methotrexate level is > 2 µmol/l (>2 x 10^{-6} M),**

INCREASE folinic acid iv as below.

For the remaining timepoints/ MTX levels follow the table below

Table for the calculation of folinic acid rescue on the basis of MTX plasma levels (Schedule 1, methotrexate 3g/m^2)

Table for the calculation of folinic acid rescue on the basis of MTX plasma levels (Schedule 1, methotrexate 3g/m^2)					
Time after starting MTX	**MTX plasma concentration (µmol/l)**				
	<0.1	0.1-2	2-20	20-100	>100
48h	None[a]	15mg/m^{2}q6h[b]	15mg/m^{2}q6h	10mg/m^{2}q3h	100mg/m^{2}q3h Consider Glucarpidase[d]
72h	None	15mg/m^{2}q6h	10mg/m^{2}q3h	100mg/m^{2}q3h Consider Glucarpidase[d]	1g/m^{2}q3h Consider Glucarpidase[d]
96h	None	15mg/m^{2}q6h	10mg/m^{2}q3h	100mg/m^{2}q3h Consider Glucarpidase[d]	1g/m^{2}q3h Consider Glucarpidase[d]
120h[c]	None	15mg/m^{2}q6h	10mg/m^{2}q3h	100mg/m^{2}q3h Consider Glucarpidase[d]	1g/m^{2}q3h Consider Glucarpidase[d]

Notes

a No extra folinic acid is required provided MTX levels are below 0.1 µmol/l (10^{-7}M) and no rise in serum creatinine at 48hours.

b Dose and schedule of folinic acid: q6h = every 6 hours.

c At time points after 120h, folinic acid administration should be continued as recommended for 120h.

d Glucarpidase administration should be a Consultant decision, taking into account renal function, kinetics and timing of MTX levels in relation to MTX infusion i.e. to consider the true '48h, 72h, 96h' levels. Blueteq approval required before use. **See APPENDIX 4 below.**

Post-hydration regimen after completion of intravenous methotrexate infusion

Continue to infuse at an approx. rate of 125 ml/m^2/hour for a minimum of 48 hours with:
1L glucose 4%, sodium chloride 0.18% containing 50 mmol of sodium bicarbonate and 20 mmol potassium chloride. (Alternating bags of sodium chloride 0.9% and glucose 5% is acceptable. Where sodium chloride 0.9% bags are used, monitor serum sodium levels)

Continue to ensure that urinary pH is above 7 by adjusting sodium bicarbonate dose.

After 48 hours from the start of the intravenous MTX, **ENSURE** a combined oral and/or intravenous intake greater than 2-3 litres/m^2/24 hours until plasma methotrexate levels **0.1µmol/l** (<1 x 10^{-7} M).

Check fluid balance at regular intervals (4-hourly) through each day, taking early action if fluid overload occurs by giving furosemide if the urine output falls below 400 ml/m^2 in any given 4-hour period.

Schedule 2 (3 hour infusion): Methotrexate administration, monitoring and Folinic Acid rescue

METHOTREXATE INFUSIONS SHOULD COMMENCE BETWEEN 0800HRS AND 1200HRS (MIDDAY). CONSULTANT ADVICE SHOULD BE SOUGHT IF THE START TIME IS LIKELY TO BE AFTER 1200HOURS. ALL SERUM MTX LEVELS SHOULD BE TAKEN AT 24 HOUR INTERVALS FROM THE DOCUMENTED START TIME OF MTX.

Methotrexate dose: 3.5g/m^2 in 0.9% saline:

500 mg/m^2 given over 15 minutes (loading dose) in 100 mls.

3000 mg/m^2 given over 3 hours in 500 ml 0.9% Saline.

Intravenous fluid schedule to be followed as per chemotherapy prescription in conjunction with strict fluid balance assessment, daily weights and renal function monitoring.

Dosage of folinic acid:

FOLINIC ACID RESCUE MUST START AT 24 HOURS FROM THE START OF METHOTREXATE.
It must be written up at the time of prescribing the MTX infusion.

Folinic acid rescue starts **24 hours** after the **start** of MTX infusion. It is administered at a dose of **30mg/m^2** intravenous push every six hours for at least 72 hours. If the patient is not vomiting, folinic acid may be given orally after the first two doses, at equivalent dose.

Monitoring Of Plasma Methotrexate Levels Following Infusion.

Times given are from time 0 (time of starting intravenous MTX infusion).

The following plasma samples are **required for patient's safe rescue** with folinic acid:

48 hours, 72 hours, and then every 24 hours if not completely rescued, i.e. until plasma methotrexate level are less than **0.1 µmol/l (**1 x 10^{-7} M).

Adjustments to dose of folinic acid rescue

Delayed MTX excretion will require increase in the dose of Folinic Acid as below.

If 48h MTX level <0.5µmol/l → standard dose folinic acid (30mg/m^2 every 6 hours)
If 48h MTX 0.5-0.99µmol /l → folinic acid 100 mg/m^2 every 6 hours
If 48h MTX >1µmol/l → folinic acid 200 mg/ m^2 every 6 hours

If 72 hour MTX > 1 µmol/l → contact Consultant and pharmacist for advice

Folinic acid dosing can also be modified if there are significant changes in renal function, independently of the MTX level. In particular the creatinine clearance at 24h post MTX infusion is critical to minimise

renal damage due to toxic MTX levels.

IF THE SERUM CREATININE INCREASES BY MORE THAN 25% from BASELINE AT 24h or 48h THEN FOLINIC ACID RESCUE SHOULD BE ESCALATED EVEN BEFORE MTX LEVEL IS KNOWN – SEEK URGENT CONSULTANT ADVICE.

CONSIDER GLUCARPIDASE ADMINISRATION IF THERE IS EVIDENCE OF SIGNIFICANT DETERIORATION IN RENAL FUNCTION AND POTENTIALLU TOXIC PLASMA MTX LEVELS – see APPENDIX 4.

Folinic acid can be discontinued once MTX levels are below 0.1 µmol/l (10^{-7}M). Please note that this should be a decision made by a Consultant or a senior ST.

Post-hydration regimen after completion of intravenous methotrexate infusion

Continue to infuse at an approx. rate of 125 ml/m^2/hour for a minimum of 48 hours with:
1L glucose 4%, sodium chloride 0.18% containing 50 mmol of sodium bicarbonate and 20 mmol potassium chloride. (Alternating bags of sodium chloride 0.9% and glucose 5% is acceptable. Where sodium chloride 0.9% bags are used, monitor serum sodium levels)

Continue to ensure that urinary pH is above 7 by adjusting sodium bicarbonate dose.

After 48 hours from the start of the intravenous methotrexate, **ENSURE** a combined oral and/or intravenous intake greater than 2-3 litres/m^2/24 hours until plasma methotrexate levels **0.1 µmol/l** (<1 x 10^{-7} M). Once MTX levels are below this value, post-hydration can be interrupted.

Check fluid balance at regular intervals (4-hourly) through each day, taking early action if fluid overload occurs by giving furosemide if the urine output falls below 400 ml/m^2 in any given 4-hour period.

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Ordering information for Voraxaze provided by Oxford Pharmacy Store, March 2022.

APPENDIX 1

Conversion table for methotrexate levels expressed in different units

Molar (M)	µmol/l
1×10^{-3}	1013.0
2×10^{-4}	202.0
1×10^{-4}	101.0
2×10^{-5}	20.0
1×10^{-5}	10.1
2×10^{-6}	2.0
1×10^{-6}	1.01
2×10^{-7}	0.2
1×10^{-7}	0.10
2×10^{-8}	0.02
1×10^{-8}	0.01

To convert methotrexate level expressed in **mol** to **g/l** multiply by 0.454

APPENDIX 2

Schedule 1 (24 hour infusion): Proforma and Guideline for the administration of Intravenous High-Dose Methotrexate 3g/m^2

Adapted for NUH use from UKALL14 protocol appendix 16. To be read together with the chemotherapy prescription.

NAME	
WARD	
UNIT NUMBER	
DOB	
TIME AND DATE OF START	

Baseline Serum Creatinine =

Time of assay (from START of Methotrexate)	TARGET level for this time point	Methotrexate level in µmol/l (as measured)	Serum creatinine at the same time as the assay	ACTION REQUIRED	SIGNATURE
48 hour	**LESS THAN 20 µmol/l**				
72 hour	**LESS THAN 2 µmol/l**				
96 hour	**LESS THAN 0.1 µmol/l**				
120 hour	**LESS THAN 0.1 µmol/l**				
144 hour	**LESS THAN 0.1 µmol/l**				

APPENDIX 3

Schedule 2 (3 hour infusion): Proforma and Guideline for the administration of Intravenous High-Dose Methotrexate 3.5g/m^2

To be read together with the chemotherapy prescription.

NAME	
WARD	
UNIT NUMBER	
DOB	
TIME AND DATE OF START	

TIMES ARE MEASURED FROM THE START OF THE METHOTREXATE INFUSION.

Baseline Serum Creatinine =

Time of assay (from START of Methotrexate)	Methotrexate level in µmol/l (as measured)	Serum creatinine at the same time as the assay	ACTION REQUIRED*	SIGNATURE
*Note that although a 24 level is often taken, particularly for patients on clinical trial protocols, the result of this level does not usually influence the FA dose, **unless the serum creatinine has changed** (discuss with Consultant if any doubt)*				
24 hour				
48 hour				
72 hour				
96 hour				
120 hour				
144 hour				

APPENDIX 4

Guidance for use of Glucarpidase (Carboxypeptidase-G2) during delayed methotrexate excretion

Glucarpidase is routinely funded by NHSE for the treatment of adults and children receiving high-dose methotrexate chemotherapy who develop a significant deterioration in renal function after the start of the high dose methotrexate, have toxic plasma methotrexate levels despite all standard rescue measures, and are at risk of life-threatening methotrexate-induced toxicities.

A significant deterioration in renal function is regarded as a serum creatinine that is at least 1.5 times the upper limit of normal and rising AND/OR a 100% rise in serum creatinine (i.e. a doubling of the pre-treatment serum creatinine value), or (rarely)_the presence of oliguria. Changes in renal function due to HD-MTX toxicity are usually noted within ≤24-48 hours of the start of the methotrexate infusion. Glucarpidase should be considered where there is delayed excretion and plasma MTX levels plateau.

Glucarpidase is a recombinant form of carboxypeptidase-G2 and works by rapidly hydrolysing methotrexate into inactive, non-cytotoxic metabolites. It reduces methotrexate levels by >98% within 15 minutes of administration. Glucarpidase is an orphan drug and not licensed in the UK.

Glucarpidase should be initiated following consultant request only. It requires prior BLUETEQ approval.

Dose and administration

Dose = 50 units/kg as a single IV dose. Multiple doses are not permitted.

Glucarpidase is supplied as vials containing 1000units. Each vial should be reconstituted (immediately prior to use) with 1ml sodium chloride 0.9% and administered over 5 minutes by bolus IV injection.

For the first 48 hours after the dose of glucarpidase, administer the same folinic acid dose given prior to glucarpidase. Administer folinic acid at least 2 hours before or 2 hours after the dose of glucarpidase.

Methotrexate concentrations within 48 hours following glucarpidase administration can only be reliably measured by a chromatographic method due to interference from metabolites. Measurement of methotrexate concentrations within 48 hours of glucarpidase administration using immunoassays results in an overestimation of the methotrexate concentration.

Glucarpidase (Voraxaze®): Ordering Instructions out-of-hours:

1. The consultant / SpR must contact the on-call pharmacist (via NUH switchboard) to advise that glucarpidase is urgently required. A Blueteq form must be submitted by the Consultant. The pharmacist must confirm that this has been approved before proceeding to order glucarpidase.
2. The pharmacist will contact Warneford Hospital switchboard on **01865 901 000** and ask to speak to the on-call pharmacist**.** NUH account numbers are 37 and 55 for QMC and City respectively. An email address is available (ops.orders@oxfordhealth.nhs.uk) however this is only manned during normal working hours. Telephone is the preferred method of contact.
3. The OPS pharmacist will **immediately** e-mail the consultant a documentation pack which contains a Patient Access form (includes prescriber information, delivery location and order quantity), advice on regulations on the use of unlicensed medicines and payment details.
4. The OPS pharmacist will request additional information including:
    - Quantity of Glucarpidase required
    - Delivery details (hospital name and address and area supply to be sent to eg. Pharmacy Department)
    - Billing Details (Hospital name and address)
    - Medical Practitioner details (Name and contact number)
    - Oncall pharmacist details (Name and contact number)

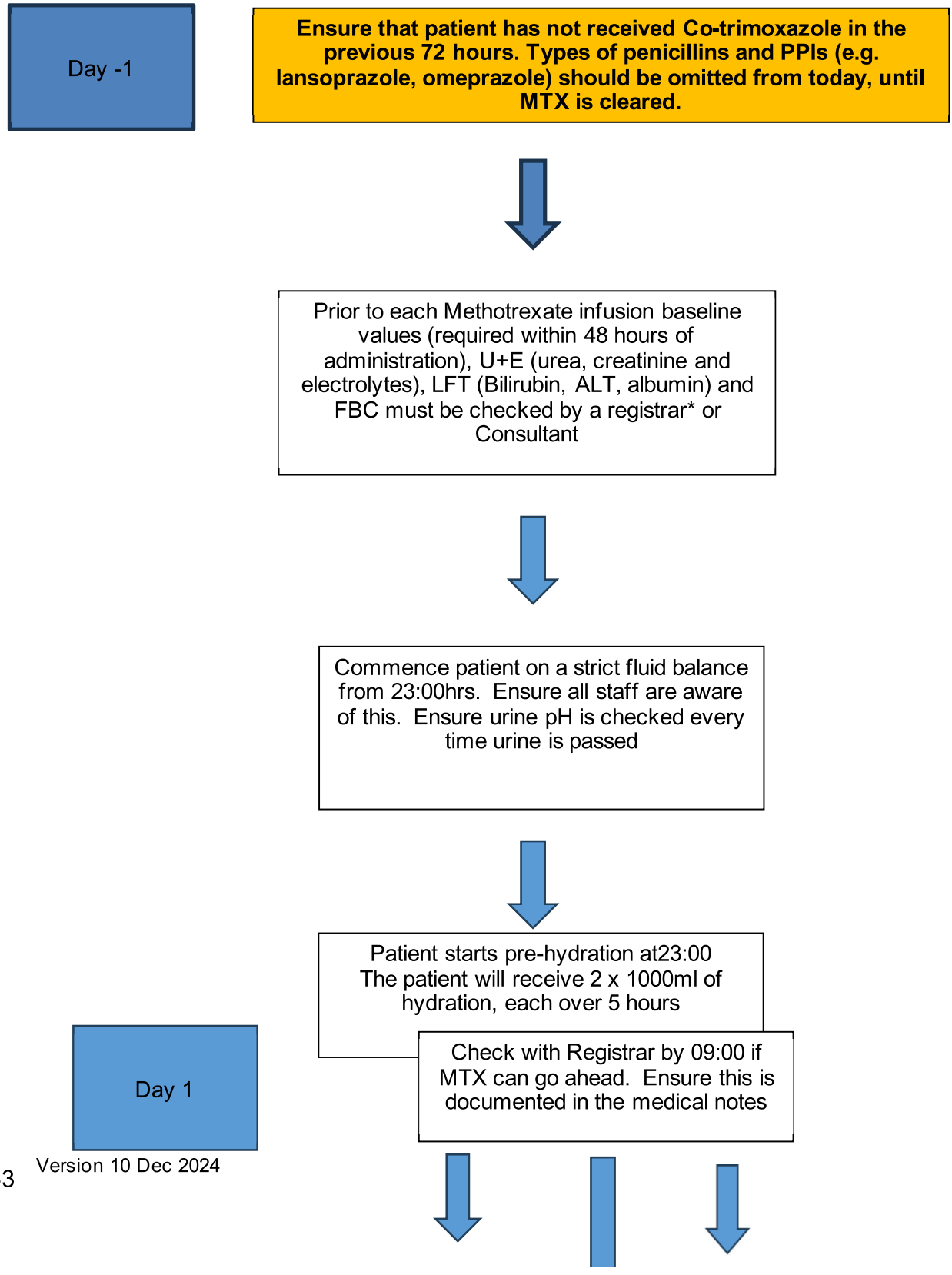
5. The consultant may want to confirm the quantity of vials to order. It is available as boxes of 2 x 1000unit vials. Dose is **50 units/kg** as a single dose. Multiple doses are not permitted.
6. The consultant should complete the Patient Access form and Signed Purchase order. These will then be e-mailed back to the OPS pharmacist **immediately**. If the signed purchase order cannot be completed, then e-mail confirmation with acceptance of the price will be sufficient.
7. Pharmacist will then be contacted by the OPS pharmacist when the order has been processed and be informed of a delivery time. Due to cost and limited needed, glucarpidase will only be ordered as required (~£27,165 for 2 x 1000unit vials). OPS will normally be able to deliver Voraxaze® within 24 hours of receipt of the order (including weekdays, weekends and bank holidays).

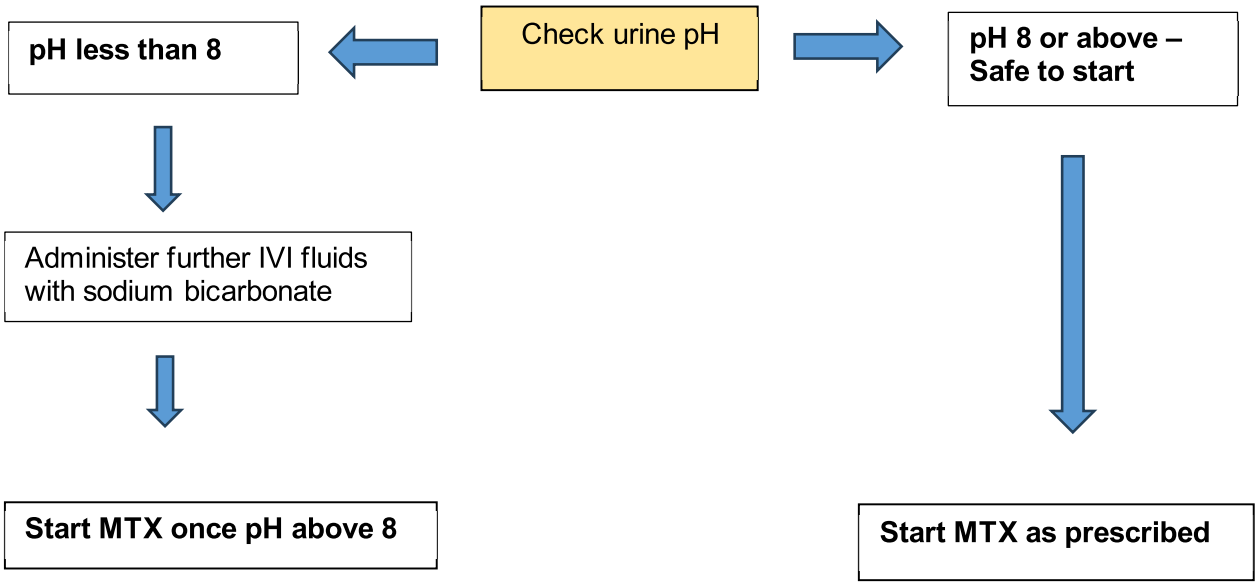
Glucarpidase (Voraxaze®): Ordering Instructions within normal working hours:

1. The consultant / SpR must contact the ward pharmacist to advise that glucarpidase is urgently required, confirming patient details and dose required.
2. Pharmacist to confirm Blueteq form submitted and approved.
3. The pharmacist will liaise with pharmacy purchasing department to place an urgent order with Oxford Pharmacy Store.

APPENDIX 5

Standard Operating Procedure for the Safe Administration of High Dose Methotrexate





Schedule 1 – ALL

Line 1 – MTX 1 hour
Line 2 - Fluids

Continue to monitor fluid balance. Maintain a urine pH of 8 or above Refer to medical team immediately

Schedule 2 – CNS Lymphoma

Line 1 – MTX – 15 minutes.
Line 2 – Fluids

MTX levels to be taken **peripherally** at **48 hours** after the start of MTX, and then every **24 hours** thereafter

MTX levels to be taken **peripherally** at **48 hours** after the start of MTX, and then every **24 hours** thereafter

Continue monitoring pH level of urine
If pH drops below 8, Registrar must be contacted immediately
Patient will require an increase in sodium bicarbonate in post-hydration fluid.
Registrar will advise/prescribe

Continue post hydration until MTX level is less than 0.1. (For Schedule 1, the levels may be acceptable at higher levels but only after discussion with Consultant)
Medical team to document in medical notes that MTX has cleared
Once this has been documented, the registrar will stop the post-hydration and folinic acid rescue

Treatment now completed

Important Considerations:

1. **Meropenem should be used if patient spikes a temperature during HD MTX infusion. Single agent only unless discussed with the Consultant**
2. **Ensure patient is not prescribed NSAIDs, Gentamicin or Amikacin. Any renal toxic medication should be omitted unless approved by the Consultant**
3. **Patient should not undergo a CT scan or MRI with contrast until MTX is fully cleared**
4. **MTX blood serum levels should be taken peripherally only**
5. **Hydration should NEVER be disconnected until MTX is fully cleared**