Glucarpidase for the Treatment of Methotrexate Induced Renal Dysfunction

Category:	Guideline
Summary:	Treatment of methotrexate induced renal dysfunction with glucarpidase, including commissioning criteria, supply route, administration, monitoring and concurrent treatment
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Distribution:	Healthcare professionals involved in care of patients treated with high dose methotrexate, including adult and paediatric oncology and haematology patients
Related Documents:	Thames Valley Cancer Alliance (TVCA) treatment protocols NHSE Clinical Commissioning Policy: Glucarpidase for the urgent treatment of methotrexate-induced renal dysfunction
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Endorsement

OUH SACTOP Committee	October 2020
OUH MMTC	February 2021
TVCA Chemo CAG	March 2022
OUH Lymphoma and Sarcoma Lead Consultants	May 2026
OUH SACTOP Committee	June 2026
OUH MMTC	June 2026
TVCA Pharmacists	June 2026

Paediatric-specific guidelines are available (TVCA Childrens network)
Guidelines for use of HIGH DOSE METHOTREXATE (HDMTX)

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Background

Adult and paediatric cancer centres use high dose methotrexate (doses greater than 1g/m^2) in chemotherapy regimens to treat cancers of both oncological and haematological natures.

As a consequence of treatment, methotrexate serum levels can be highly elevated. Extremely high levels of methotrexate can lead to precipitation of the drug in the renal tubules, delayed drug clearance, and the potential for acute renal failure. As a result, patients may be exposed to potential life-threatening toxicities including myelosuppression, mucositis, hepatotoxicity and dermatitis.

To guard against toxicity, high dose methotrexate regimes must contain concurrent treatment with aggressive hydration, urine alkalinisation and use of folinic acid rescue. Despite this, cases of severe and life-threatening nephrotoxicity can still occur.

NHS England (NHSE) has commissioned use of glucarpidase (Voraxaze®) for the **urgent treatment of methotrexate-induced renal dysfunction**.

Glucarpidase is a recombinant form of the bacterial enzyme carboxypeptidase G2 and works by rapidly hydrolysing methotrexate into inactive non-cytotoxic metabolites that can be cleared by alternative routes of elimination. Glucarpidase provides effective rescue from toxicity by reducing methotrexate levels by greater than 98% within 15 minutes of administration.

Routine prevention of methotrexate induced renal dysfunction

Please use the relevant TVCA / NSSG treatment protocol to guide routine toxicity prevention measures.

SACT protocols using high dose methotrexate should include full details on initiation of adequate hydration protocol prior to, and during methotrexate treatment and an embedded protocol for urine alkalinisation prior to, and during treatment using sodium bicarbonate or acetazolamide.

Protocols will also include recommendations on urine output, blood count, urine pH and therapeutic drug monitoring timeframes and targets, including recommendations on thresholds for intervention and requirement for strict fluid balance.

There are recommendations for early methotrexate infusion timing and emphasis on time urgency of blood sampling, interpretation and action.

SACT protocols should further include details on initiating calcium folinate rescue therapy (e.g. 24, 36 or 42 hours after the initiation of methotrexate infusion) and subsequent dose adjustment according to symptoms of toxicity and methotrexate levels.Drug interactions are frequently implicated in the development of toxicity, known interactions should be avoided wherever possible.

DO NOT prescribe nephrotoxic drugs or drugs that may reduce methotrexate excretion

e.g. NSAIDS, ciprofloxacin, co-trimoxazole, gentamicin, penicillin, probenecid, omeprazole, piperacillin-tazobactam. This list is not exhaustive – please check for drug interactions and discuss with treating consultant and pharmacist

Urgent treatment of methotrexate induced renal dysfunction

Even moderate deterioration in renal function may cause a significant reduction in methotrexate clearance. Early toxicity can be asymptomatic but can sometimes present with mild nausea and vomiting, raised creatinine and reduced urine output.

Any deterioration in renal function more than 1.5 x the baseline creatinine value should be reported to the senior consultant in charge immediately, including out of hours. Check for appropriate fluid administration rates, calcium folinate administration times, drug interactions and urine output.

Enhanced rescue measures generally include increased frequency and/or dose of calcium folinate, forced diuresis through continued and/or increased intravenous fluids and further optimisation of urine alkalinisation as methotrexate renal excretion is highly pH sensitive.

Where rescue measures are unsuccessful, glucarpidase should be considered at the earliest opportunity.

Indication for glucarpidase:

NHSE will commission glucarpidase in patients receiving high dose methotrexate (greater than 1g/m^2) who:

- Develop a significant deterioration in renal function after the start of methotrexate (serum creatinine that is at least 1.5 times **baseline*** and rising, or the presence of oliguria), **AND**
- Have toxic plasma methotrexate levels**, **AND**
- Have had optimisation of all other supportive measures, **AND**
- Are at risk of life-threatening methotrexate-induced toxicities

* For the avoidance of doubt, **baseline creatinine** should be taken as the creatinine result on the day before treatment.

** Defining a toxic methotrexate level is complicated by the regimen used and the time at which the level is tested. However, patients must have a dangerously high blood methotrexate level that is elevated relative to the expected level at that time point despite all standard rescue measures or renal function are decreasing. Refer to the relevant protocol and SmPC for further guidance. Consider using the MTXPK.org Simulation Tool to help understand the pharmacokinetics of high-dose methotrexate, especially regarding delayed clearance. Discuss with the consultant as appropriate.

Prompt action is imperative. The ward pharmacist (or on-call pharmacist if out of hours) should be alerted to the possibility of need for glucarpidase immediately.

Due to its high cost, treating clinicians must follow local processes to ensure the patient meets the commissioning criteria and that they have Trust approval for use.

Please follow local formulary approval process. For example, this may include urgently contacting the Chair (or delegated deputy) of the Medicines Management and Therapeutics Committee (MMTC), or the equivalent authority for authorisation.

The treating clinician should confirm that the patient meets the commissioning criteria and that the treatment cost will be reimbursed by NHSE. **A Blueteq form (GLU1) must be completed to enable reimbursement.**

Glucarpidase dose

Glucarpidase (Voraxaze®)
50 units/kg via intravenous injection over 5 minutes.
See Table 1 for recommended dose banding in adults
Multiple doses are not permitted.

Table 1 - Recommended glucarpidase dose banding [5]

Weight (kg)	Vials
20kg or under	1
21 - 40	2
41 - 60	3
61 - 80	4
81 - 100	5
101 - 120	6
121 - 140	7
141 – 160*	8

* Continue to dose patients weighing more than 160kg according to their weight

Dose modification

- Renal dose adjustment is not required.
- Information is not available for hepatic dose adjustment.

Formulation

- Glucarpidase powder for solution for injection 1000units per 1 mL vial.
- **Requires fridge storage (2 - 8°C)**
- Do not freeze.

Adverse Effects

Most common (affects 1 in 10 people):

- Burning sensation
- Headache
- Paraesthesia (sensations like numbness, tingling, pins and needles)
- Flushing and feeling hot.

For the full list of side effects and restrictions of glucarpidase, see the package leaflet.

Drug Interactions

Glucarpidase can decrease calcium folinate (folinic acid) concentrations, which may decrease their rescue effect.

Glucarpidase may also reduce the concentrations of other folate analogues or folate analogue metabolic inhibitors.

Obtaining Glucarpidase

Glucarpidase is not stocked across TVCA hospitals due to high cost and infrequent use. Stock must be obtained directly for individual patients.

Oxford Pharmacy Store (OPS) supply glucarpidase and will dispatch between 9am-10pm on weekdays and 9-5pm on weekends and bank holidays. **01865 904141 or email ops.orders@oxfordhealth.nhs.uk (9am – 5pm Monday to Friday) / 01865 901000 (out of working hours – ask to speak to the OPS team).**

Please note OPS is not a part of Oxford University Hospitals, they are affiliated with Oxford Health NHS Foundation Trust and contact details are relevant for all TVCA sites. OUHFT staff should also refer to Appendix 1 specific Trust procedure.

Administration

1. **Do not administer folinic acid for 2 hours before and for 2 hours after glucarpidase dose** (folinic acid is also a substrate for glucarpidase, therefore co-adminstration may reduce efficacy).
2. Flush the line before administration of glucarpidase
3. Reconstitute each vial of glucarpidase with 1 mL sodium chloride 0.9%
4. Roll and tilt the vials gently to mix. Do not shake.
5. Draw up the required volume and administer immediately as a bolus injection over 5 minutes.
6. Flush the line again following administration.

Continued Monitoring and Supportive Therapies

For the first 48 hours following glucarpidase administration, standard immunoassays are inaccurate for determining serum methotrexate levels.

Serum Creatinine must be monitored closely to guide response.

A high performance chromatography (HPLC) method is recommended for measuring MTX concentrations following glucarpidase administration. In the absence of HPLC assay it is recommended that calcium folinate should be continued at the same dose as pre-administration of glucarpidase for 48 hours post glucarpidase administration, then revert to dosing in line with methotrexate levels.

Calcium folinate, hydration and alkalinisation of urine should be continued until serum methotrexate levels are below the specified level as determined in the relevant SACT protocol.

References

1. Protherics Medicines Development Ltd. Summary of Product Characteristics: Voraxaze. Last updated: 15/06/2023. [Online] Available from: https://products.mhra.gov.uk/ (accessed 23/04/2026)
2. SERB SAS. Summary of Product Characteristics: Glucarpidase (Voraxaze). [Online] Available from: https://www.ema.europa.eu/en/documents/product-information/voraxaze-epar-product-information_en.pdf (accessed 23/04/2026)
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4. European Medicines Agency (EMA). Voraxaze (glucarpidase): An overview of Voraxaze and why it is authorised in the EU. EMA/748968/2021; updated 01/2022. [Online] Available at: https://www.ema.europa.eu/en/documents/overview/voraxaze-epar-medicine-overview_en.pdf (accessed 23/04/2026)
5. BTG Specialty Pharmaceuticals. Voraxaze dosing and administration. [Online] Available at: https://voraxaze.com/dosing-and-administration (accessed 23/04/2026)
6. Oxford Pharmacy Stores. Voraxaze Ordering Sheet UK. January 2026.

Appendix 1 – Oxford University Hospitals FT (OUHFT) process for obtaining Glucarpidase (Voraxaze®)

Other TVCA sites should contact OPS directly – liaise with your hospital stores / purchasing department.

This order process is directly applicable only to OUHFT

1. Consultant to contact the cancer pharmacist or on-call pharmacist out of hours, to advise that glucarpidase is urgently required.
2. Consultant to complete Blueteq form, confirming that patient meets the commissioning criteria, to gain approval to proceed. During working hours, a discussion with the advanced cancer pharmacist for the relevant disease (e.g., sarcoma, lymphoma, myeloid), highly advanced oncology/haematology pharmacist, as well as the MMTC chair (or delegated deputy) is recommended.
3. Pharmacist to review relevant SACT protocol, checking the timing of methotrexate levels and that patient meets commissioning criteria. If this is requested out of hours, the senior on call pharmacist should be involved.
4. Pharmacist to confirm the quantity of vials to order with the treating consultant, noting;
    a. Available as a single 1000 unit vial (item code VOR002)
    b. The dose is 50 units/kg as a single dose
    c. Multiple doses are not permitted
5. Pharmacist to raise order with Pharmacy Purchasing & Distribution Unit (PPDU), or if out of hours to contact on-call PPDU for support
6. PPDU to contact Oxford Pharmacy Stores (OPS) via **01865 904141 (9am — 5pm Monday to Friday)** or the emergency order line: **01865 901000 (5 – 10pm Monday to Friday AND 9am – 5pm Weekends / Bank Holidays)** asking for the OPS team. Quote the patient's initials, delivery site address, billing site address,prescriber's name and contact number, and on-call pharmacist name and contact number
7. PPDU / Pharmacist will then be contacted by OPS when the order has been processed and be informed of a delivery time. Due to cost and limited need, glucarpidase will only be ordered as required. OPS will aim to dispatch within 24 hours of order. In view of proximity to OUHFT, the delivery times are usually quicker.
8. Pharmacist to inform the advanced cancer pharmacist for the relevant tumour site (if not already involved), as well as the Medicines Effectiveness team that glucarpidase has been used.
9. Medicines Effectiveness team will retrospectively ensure that the trust is reimbursed as per commissioning policy.
10. Each case may be subject to retrospective review to ensure appropriate glucarpidase use and collate learning points for feedback.