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
Valid From:	February 2022
Date of Next Review:	February 2025
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

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

Contents

Background

Adult and paediatric cancer centres may use high dose methotrexate (doses greater than 1g/m2) 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, muscositis, 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.

Glucarpidase (Voraxaze®) is an orphan medicine, not licensed in the UK. NHS England (NHSE) has commissioned use for the **urgent treatment of methotrexate-induced renal dysfunction**. Due to it's unlicensed nature, this is only available on a named-patient basis.

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 alkinisation 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 24 hours (or 36 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, 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 1.2 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 alkinisation 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/m2) who:

- Develop a significant deterioration in renal function after the start of methotrexate (serum creatinine ≥ 1.5xULN and rising, or the presence of oliguria)
- Have toxic plasma methotrexate levels (as defined in individual protocols at specified time point)
- Have had optimisation of all other supportive measures
- Are at risk of life-threatening methotrexate-induced toxicities

A Blueteq form (Appendix 2) **should be completed at the point of prescribing** to confirm the patient meets the commissioning criteria and to permit Trust cost reimbursement.

Prompt action is essential. **The ward pharmacist (or on-call pharmacist) should be immediately alerted of the need for Glucarpidase.**

In exceptional circumstances out of hours and due to it's emergency indication, the form may be completed retrospectively with the ordering pharmacist confirming eligibility criteria has been met, with follow up of Blueteq completion on the next working day. This is a high cost drug (more than £50k per patient).

Local Trust formulary processes should be adhered to. 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.

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 ADULT dose banding [5]

Weight (kg)*	Vials
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 1ml 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 Voraxaze, see the package leaflet.

Drug Interactions

Glucarpidase can decrease leucovorin concentrations, which may decrease the effect of leucovorin rescue.

Glucarpidase may also reduce the concentrations other folate analogs or folate analog metabolic inhibitors.

Obtaining Glucarpidase

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

Oxford Pharmacy Stores (OPS) supply glucarpidase and will dispatch 24 hours a day: **01865 904141 (9am – 5pm) / 01865 901000 (OOH via on-call pharmacist).**

Please note OPS is not a part of Oxford University Hospitals, they are affiliated with Oxford Health 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 1ml sodium chloride 0.9%
4. Roll and tilt the vials gently to mix. Do not shake.
5. Draw up the required volume and give 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.

Calcium folinate should be continued at the same dose as pre-administration of Glucarpidase during this 48 hours, then revert back to dosing in line with methotrexate levels.

Calcium folinate, hydration and alkalisation of urine should be continued until serum methotrexate level are less than 0.1micromol/L for 3 consecutive days

References

1. Protherics Medicines Development Ltd. Summary of Product Characteristics: Voraxaze. January 2013. [Online] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125327lbl.pdf (accessed 20/04/2022)
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3. Clinical Commissioning Policy: Glucarpidase for the urgent treatment of methotrexate-induced renal dysfunction. NHS England B15/P/a. January 2015. [Online] Available from: https://www.england.nhs.uk/wp-content/uploads/2018/07/Glucarpidase-for-the-urgent-treatment-of-methotrexate-induced-renal-dysfunction.pdf (accessed 20/04/2022)
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 20/04/2022)
5. BTG Specialty Pharmacueticals. Voraxaze dosing and administration. [Online] Available at: https://voraxaze.com/dosing-and-administration (accessed 20/04/2022)

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

Other TVCA sites should contact OPS directly:

01865 904141 (9am – 5pm) / 01865 901000 (OOH via on-call pharmacist)
Liaise with your local hospital stores / purchasing department

This order process is directly applicable only to OUHFT

1. Consultant to contact the ward pharmacist, or on-call pharmacist out of hours, to advise that Glucarpidase is urgently required.
2. Consultant to discuss with MMTC chair (or delegated deputy) and gain approval to proceed (including out of hours).
3. Pharmacist to confirm the quantity of vials to order with the treating consultant, noting;
    a. Available as a single 1000unit vial (item code VOR001)
    b. The dose is 50units/kg as a single dose
    c. Multiple doses are not permitted
4. Pharmacist to raise order with PPDU, or if out of hours to contact on-call PPDU for support
5. PPDU or on-call pharmacist to contact Oxford Pharmacy Stores (OPS) via **01865 904141 (9am – 5pm)** or the emergency order line: **01865 901000** asking for the on-call pharmacist. Quote the patient's initials, delivery site address, billing site address and prescriber's name.
6. 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 normally be able to deliver Voraxaze® within 24 hours of receipt.
7. Pharmacist must complete a "Non-formulary SharePoint form" (can be done on next working day if request to supply is out of hours)
8. Medicines Effectiveness team will retrospectively ensure that funding is recouped from NHSE as per commissioning policy

Appendix 2 – Blueteq NHSE criteria for funding

At point of prescribing, a **Blueteq form** should be completed to allow cost reimbursement. Please check Blueteq for the most recent form, version 1 criteria can be seen below.

In exceptional out of hours emergencies where Blueteq cannot be immediately accessed, forms may be completed retrospectively by the clinician due to the emergency indication.

Patient eligibility should be confirmed by the ordering pharmacist and completion of form followed up on the next working day.

GLUC1 – NHS England - Initial Funding Application - Glucarpidase for the urgent treatment of high dose methotrexate-induced renal dysfunction

1. I confirm that this application is being made by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.	○ Yes ○ No * Required
2. I confirm the indication the patient received high-dose (usually defined as a dose >1g/m2) methotrexate chemotherapy for is either: ○ Acute Lymphoblastic lymphoma (ALL), or ○ Sarcoma, or ○ High-grade lymphomas, or ○ Other * Required	○ Yes ○ No * Required
3. I confirm if the patient is an adult or a child. If the patient is a child, please enter the patients age below ○ Adult ○ Child * Required Age of Child: [ ] * Required	○ Yes ○ No * Required
4. I confirm the patient is at risk of life-threatening methotrexate induced toxicities.	○ Yes ○ No * Required
5. I confirm the patient has developed significant deterioration in renal function* after the start of high-dose methotrexate treatment and has dangerously high blood methotrexate level relative to the expected level at that time point that is rising despite all standard rescue measures. Note: A significant deterioration in renal function is regarded as a serum creatinine that is at least 1.5 times baseline and rising, or the presence of oliguria.	○ Yes ○ No * Required
6. I confirm rescue measures have been optimised (e.g use of fluids and calcium folinate) and failed.	○ Yes ○ No * Required
7. I confirm I understand that glucarpidase is only commissioned for a single dose per patient. Please enter the dose of glucarpidase to be given: [ ] * Required Note the recommended dose is 50 Units per kilogram	○ Yes ○ No * Required