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Newcastle University

Health Technology Briefing
March 2022

Glucarpidase for methotrexate toxicity

Company/Developer	Protherics Medicines Development Ltd (part of BTG Specialty Pharmaceuticals)

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 1684	NICE ID: 10761	UKPS ID: 664065

Licensing and Market Availability Plans

Completed phase II clinical development.

Summary

Glucarpidase has been developed to reduce toxic plasma methotrexate concentration in adults and children with delayed methotrexate clearance or at risk of methotrexate toxicity. Methotrexate is a drug that is used to treat certain cancers. With methotrexate, cancer cells can no longer make DNA, which kills cancer cells. However, methotrexate can also be harmful to other normal cells and organs in the body. This harmful effect is called methotrexate toxicity. The longer methotrexate stays in the body, the higher the risk of toxicity. Risk factors for methotrexate toxicity include a history of kidney dysfunction, volume depletion, acidic urine, and drug interactions. Methotrexate toxicity leads to morbidity and occasional mortality but may also interrupt cancer treatment. There are currently no medicinal products available to rapidly decrease toxic methotrexate concentrations. The only options available are extracorporeal methods (e.g., haemodialysis), which show limited efficacy and have a high risk of rebound toxicity.

Glucarpidase is a protein that can transform methotrexate in the blood into harmless substances. Thus, the amount of methotrexate in the blood is lowered, and the risk of toxicity is reduced. Since glucarpidase does not enter cells, it does not stop any methotrexate already inside cancer cells from treating the cancer. If licenced, glucarpidase will provide an effective treatment option for patients at risk of methotrexate toxicity.

Proposed Indication

The management of patients with delayed methotrexate clearance or intrathecal methotrexate overdose.[1]

Technology

Description

Glucarpidase (Voraxaze), previously known as carboxypeptidase G2, is a carboxypeptidase G2 enzyme that hydrolyses the terminal glutamate residue from methotrexate.[2] Glucarpidase hydrolyses methotrexate rapidly to the inactive metabolites DAMPA (4-[[2,4-diamino-6-(pteridinyl)methyl]-methylamino]-benzoic acid) and glutamate in patients with methotrexate-induced nephrotoxicity and delayed methotrexate excretion.[3] It has been shown that the conversion of methotrexate to DAMPA relieves stress on the kidneys for elimination of methotrexate, by providing an alternative route of elimination, and generates a relatively nontoxic compound.[4]

Glucarpidase has been developed for the management of patients with delayed methotrexate clearance or intrathecal methotrexate overdose. In the phase II clinical trial (NCT00219791), glucarpidase was administered at a dose of 50 Units per kilogram (kg).

Key Innovation

Current treatment options for methotrexate toxicity, such as folinic acid, do not always prove to be effective for some patients.[5] Where increased supportive care (folinic acid, urine alkalinisation and fluid hydration) is failing and toxicity persists, there is currently no effective medicinal product available to treat toxic methotrexate levels. The only options available are extracorporeal methods, such as haemodialysis, which can show limited efficacy, are invasive for the patient and carry a risk of bleeding and infection.[6,7] Patients treated with extracorporeal methods are also at a high risk of methotrexate rebound toxicity and these methods can lead to several complications in critically ill patients who are at higher risk for electrolyte abnormalities.[8] There is therefore a high unmet clinical need for a safe, effective and rapid rescue treatment to clear methotrexate and avoid further complications.

Glucarpidase has shown high efficacy in reducing toxic methotrexate concentrations in patients with delayed methotrexate elimination. A study involving patients receiving methotrexate as treatment for various cancers showed a rapid and sustained reduction (95.6%–99.6%) in plasma methotrexate levels within 15 minutes after administration of glucarpidase.[9] If licenced, glucarpidase will be a treatment option capable of inducing an effective and fast reduction of methotrexate levels in patients at risk of methotrexate toxicity who do not show improvement with supportive care.[6]

Regulatory & Development Status

Glucarpidase has been authorised in the EU under exceptional circumstances to reduce toxic plasma methotrexate concentration in adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity.[10]

Glucarpidase was designated an orphan drug in the EU in 2003 for the adjunctive treatment of patients at risk of methotrexate toxicity.[5] The orphan designation for glucarpidase was maintained in 2021.[11]

Glucarpidase is currently in phase II/III clinical development for patients who have been treated with high-dose methotrexate for central nervous system lymphoma, diffuse large B-cell lymphoma and acute lymphoblastic leukemia.[12]

Patient Group

Disease Area and Clinical Need

Methotrexate is one of a group of chemotherapy drugs called anti-metabolites and is used as a treatment for a number of different types of cancer.[13] It is an antineoplastic agent, usually administered alone or as part of a combined chemotherapy regimen. In some prevalent cancers like non-Hodgkin lymphoma, acute lymphoblastic leukaemia (ALL) and osteosarcoma, methotrexate is used at high doses (> 500 mg/m2). High-dose methotrexate can be safely administered accompanied by supportive care measures (hyperhydration, urine alkalinisation, high-dose leucovorin) to enhance the solubility of methotrexate and its metabolites in urine and prevent the potential toxicity of methotrexate.[14,15] Although high-dose methotrexate is usually well tolerated, some patients develop nephrotoxicity, due to the crystallisation and precipitation of methotrexate and its metabolites in the renal tubules. Nephrotoxicity can lead to delayed methotrexate elimination and prolonged exposure to high plasma levels of methotrexate. This is a life-threatening condition that can lead to severe systemic methotrexate toxicities and may also interrupt cancer treatment, potentially leading to inferior anticancer outcomes.[7] Vomiting and diarrhoea during or shortly after the administration of methotrexate have been observed in patients who developed methotrexate toxicity, but the majority of patients with renal dysfunction are initially asymptomatic, and most present with nonoliguric renal dysfunction.[14] Risk factors for methotrexate-associated toxicity include a history of renal dysfunction, volume depletion, acidic urine, and drug interactions.[7]

Although high-dose methotrexate is safely administered to most patients, it has been estimated that it can cause significant toxicity, including acute kidney injury in 2%–12% of patients.[7] Methotrexate toxicity affects approximately 0.3 in 10,000 people in the EU.[5]

Recommended Treatment Options

Folinic acid and levofolinic acid (an isomer of folinic acid) are currently recommended by the National Institute of Health and Care Excellence (NICE) for the prevention of methotrexate-induced adverse events and can be administered to treat acute methotrexate toxicity.[16,17] However, folinic acid is less effective at high methotrexate plasma concentrations (>10 micromolar).[15]

Since January 2015, an NHS England Clinical Commissioning Policy (CCP) has been in place for Glucarpidase for the urgent treatment of methotrexate-induced renal dysfunction. In cases where all other supportive measures (such as the use of fluids and folinic acid) have been optimised, this CCP allows for the routine funding of glucarpidase for the treatment of adults and children receiving high-dose methotrexate chemotherapy (doses > 1 g/m2) who develop a significant deterioration in renal function after the start of the high dose methotrexate, have toxic plasma methotrexate levels and, despite rescue measures (e.g. folinic acid), are at risk of life threatening methotrexate induced toxicities. The CCP also acknowledges that there are no other drugs currently used for the same indication.[18] Glucarpidase is also included in the Royal College of Emergency Medicine and National Poisons Information Service Guideline on Antidote Availability for Emergency Departments.[19]

Clinical Trial Information

Trial	NCT00219791; Study of Recombinant Carboxypeptidase G2 (CPG2) for the Management of Patients with Delayed Methotrexate (MTX) Clearance or Intrathecal MTX Overdosage **Phase II** – Completed

	Location – 1 EU country **Study completion date** – June 2003
Trial Design	Non-randomised, single group assignment, open label
Population	Patients with impaired methotrexate (MTX) clearance; Patients receiving high-dose MTX for treatment of acute lymphoblastic leukaemia, non-Hodgkin lymphoma or a solid tumour; Aged 18 years and older
Intervention(s)	Glucarpidase 50 units/kg
Comparator(s)	No comparator
Outcome(s)	Primary outcome: Reduction in serum MTX concentration See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT00634504; An Open-Label Study to Assess the Pharmacokinetics of Leucovorin in Patients Receiving High Dose Methotrexate, With or Without Voraxaze Treatment **Phase I** – Completed **Location** – US **Study completion date** – August 2009
Trial Design	Non-randomised, parallel assignment, open label
Population	Patients receiving high-dose MTX and require intravenous leucovorin
Intervention(s)	Glucarpidase, high-dose methotrexate and leucovorin
Comparator(s)	High-dose methotrexate and leucovorin
Outcome(s)	Primary outcome: Pharmacokinetics of leucovorin [Time frame: 3 hours post LV administration] See trial record for full list of other outcomes.
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of glucarpidase was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Glucarpidase for the urgent treatment of methotrexate induced renal dysfunction. B15/P/a. January 2015.

Other Guidance

- Clatterbridge Cancer Centre NHS Foundation Trust. Glucarpidase (Voraxaze®) Treatment of High Dose Methotrexate Toxicity. 2021.[20]
- Gloucestershire Hospitals NHS Foundation Trust. Glucarpidase (Voraxaze®) for the Treatment of Methotrexate-induced Renal Dysfunction. 2021.[21]
- Royal College of Emergency Medicine. Service Guideline on Antidote Availability for Emergency Departments. 2021.[19]
- Ramsey LB et al. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. 2018.[15]
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Additional Information

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