HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
20 JULY 2022

The legally binding text is the original French opinion version

glucarpidase
VORAXAZE 1,000 units powder for solution for injection

First assessment

Key points

Favourable opinion for reimbursement as treatment to reduce toxic plasma methotrexate concentration in adults and children with delayed methotrexate elimination or at risk of methotrexate toxicity.

What therapeutic improvement?

Therapeutic improvement in the management of the condition.

Role in the care pathway?

In all cases of use of high-dose methotrexate (MTX HD), it is necessary to promote its elimination using hyperhydration, to stop medicinal products that could reduce methotrexate clearance (nonsteroidal anti-inflammatories, penicillin and its derivatives, salicylates, probenecid, gemfibrozil, trimethoprim-sulfamethoxazole, amphotericin, aminoglycosides, proton pump inhibitors) and urine alkalinisation and to implement close monitoring of kidney function and methotrexate concentrations.

The administration of folinic acid (calcium folinate or levofolinate), which works by displacing intracellular methotrexate into the blood compartment and helping to restore low intracellular folate reserves, is recommended 24 to 36 hours after treatment with MTX-HD until the elimination of MTX, with the dosage regimen being strongly dependent on the dosage, the patient's renal function and plasma methotrexate concentrations. However, it should be noted that treatment with folinic acid is less effective at high concentrations of MTX (> 10 µmol/L for ≥ 48 hours), requiring a dose increase. Nonetheless, its use is limited by the maximum administrable dose, due to the high calcium content, exposing patients to a risk of cardiac and neurological disorders. Finally, renal dialysis methods may be considered. Standard haemodialysis and peritoneal dialysis have not been shown to be effective in the elimination of methotrexate. High-flow haemodialysis, haemoperfusion and acute intermittent haemodialysis using a high-flow dialyser have demonstrated efficacy on methotrexate clearance. However, these methods are not an optimal treatment solution given the pharmacokinetic characteristics of methotrexate, exposing patients to a risk of MTX concentration rebound phenomena.

Role of the medicinal product in the care pathway

VORAXAZE (glucarpidase) is a rescue treatment that should be used to reduce toxic methotrexate concentrations when patients have delayed methotrexate elimination or present a risk of methotrexate toxicity, defined as impaired renal function or evidence of delayed MTX elimination.

It should be noted that in 2018, an international expert consensus published specific guidelines for the use of glucarpidase in acute renal failure leading to delayed MTX elimination. The main recommendations include:

- The administration of glucarpidase (at a dose of 50 U/kg) should be performed within 48 to 60 hours following the start of MTX HD infusion, in order to limit toxicities;
- The administration of glucarpidase should be performed following an interval of 2 hours after the last folinic acid infusion in order to prevent any interactions, since the latter is a glucarpidase substrate in the same way as MTX;
- The administration of folinic acid should be resumed and continued for at least 2 hours following the administration of glucarpidase until MTX concentrations are below 0.1-0.2 µmol/L;
- Calcium levofolinate or disodium levofolinate should be preferred to calcium folinate in order to reduce the administered dose and calcium concentrations;
- The assay of residual methotrexate concentrations after glucarpidase should be performed using an HPLC method enabling the chromatographic separation of MTX and DAMPA (its main metabolite), to avoid any interference (this is not the case with other immunoenzymatic assay methods);
- Assay of plasma methotrexate concentrations and the administration of folinic acid should be continued for at least 48 hours following the administration of glucarpidase due to the MTX release phenomenon and the risk of rebound toxicity;
- Following MTX infusion, toxicity is expected when the plasma concentrations exceed the following limits (associated with elevated serum creatinine):
    - At the dose of 1 to 8 g/m2 administered for 24 to 42 hours: concentrations > 120 µmol/L at 24h, > 30 µmol/L at 36h, > 10 µmol/L at 42h and > 5 µmol/L at 48h
    - At the dose of 8 to 12 g/m2 administered for ≤ 6 hours: concentrations > 50 µmol/L at 24h, > 30 µmol/L at 36h, > 10 µmol/L at 42h and > 5 µmol/L at 48h
- If glucarpidase is not available:

- Treatment with folinic acid remains the best option to be used within 60 hours following the start of infusion of MTX HD;

- In the event of high MTX concentrations, certain renal dialysis methods may be considered, with the expected benefits outweighing the risks associated with these techniques.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Renal toxicity related to the use of high doses of methotrexate can result in prolonged exposure to MTX, particularly in the event of pre-existing renal impairment or a risk of delayed elimination. It is a medical emergency, which can cause severe toxicities and be life-threatening.

◗ The proprietary medicinal product VORAXAZE (glucarpidase) is a curative and preventive medicinal product.

◗ Considering the capacity of glucarpidase to rapidly reduce toxic plasma methotrexate concentrations and the safety profile deemed to be acceptable, the efficacy/adverse effects ratio is high.

◗ There are therapeutic alternatives, which are not numerous and present limitations and risks relative to their use (see section 05 of this opinion)

VORAXAZE (glucarpidase) is a rescue treatment that should be used to reduce toxic methotrexate concentrations when patients have delayed methotrexate elimination or present a risk of methotrexate toxicity (see section 08 of this opinion).

Public health benefit

Considering:

- the seriousness of the medical situation in question (life-threatening emergency) and its low incidence;
- the medical need very partially met by the few available alternatives and considering the limitations and risks related to their use;
- the lack of additional response to the identified medical need given:
    - the capacity of glucarpidase to rapidly reduce toxic methotrexate concentrations demonstrated in the PR001-CLN-001, 002, 003 and 006 non-comparative compassionate-use studies;
    - but the absence of a demonstrated additional impact on morbidity and mortality, in particular in terms of the reversibility of renal damage and the extra-renal consequences of use of MTX HD in patients at risk of delayed methotrexate elimination or at risk of methotrexate toxicity;
- and the lack of expected impact on the organisation of care;

VORAXAZE (glucarpidase) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of VORAXAZE (glucarpidase) is substantial in the MA indication.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.

Clinical Added Value

Considering:

- **the efficacy results from four non-randomised, non-comparative, open-label compassionate-use studies (studies 001, 002, 003 and 006), as well as the grouped analysis performed, suggesting the efficacy of glucarpidase on the rapid achievement of a reduction in methotrexate concentrations for the majority of patients, as well as an improvement in renal function;**

but considering, on the other hand:

- **the limitations of these studies, with an impact on the interpretability of the results and assessment of the effect size, in particular the low number of patients and the numerous missing data, as well as the high level of heterogeneity between these studies (particularly in terms of inclusion criteria, definition of delayed MTX elimination, administration of glucarpidase and authorised concomitant treatments);**
- **the low number of patients included in some studies, particularly paediatric patients;**
- **a safety profile that is difficult to evaluate due to the numerous adverse events related to the cancer and/or the toxicity of MTX, but nonetheless deemed to be satisfactory in view of the seriousness of these situations which can be life-threatening;**
- **the absence of long-term efficacy and safety data given the short follow-up of patients in the clinical studies submitted;**

the Committee considers that VORAXAZE (glucarpidase) provides a minor clinical added value (CAV IV) in the care pathway for the treatment of methotrexate-related toxicities in patients with delayed methotrexate elimination or at risk of methotrexate toxicity.