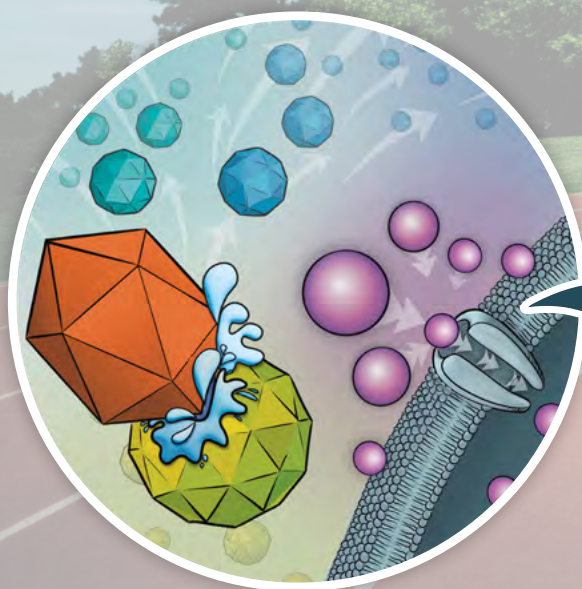


# VORAXAZE® AND LEUCOVORIN:

## UNDERSTANDING THEIR UNIQUE AND ESSENTIAL ROLES IN MANAGING MTX TOXICITY IN PATIENTS WITH DELAYED CLEARANCE DUE TO RENAL IMPAIRMENT

**CLEAR THE HURDLE OF DELAYED METHOTREXATE CLEARANCE  
DUE TO ACUTE KIDNEY INJURY WITH VORAXAZE<sup>1</sup>**



**LOOK INSIDE**  
to follow a visual storyline and  
discover more about these agents'  
complementary roles.

### Indication and Limitations of Use

- Voraxaze® is a carboxypeptidase indicated to reduce toxic plasma methotrexate concentration (greater than 1 micromole per liter) in adult and pediatric patients with delayed methotrexate clearance (plasma methotrexate concentrations greater than 2 standard deviations of the mean methotrexate excretion curve specific for the dose of methotrexate administered) due to impaired renal function
- Limitations of Use: Voraxaze® is not recommended for use in patients who exhibit the expected clearance and expected plasma methotrexate concentration. Reducing plasma methotrexate concentration in these patients may result in subtherapeutic exposure to methotrexate

### Important Safety Information

#### Warnings and Precautions

##### Serious Hypersensitivity Reactions

- Serious hypersensitivity reactions, including anaphylactic reactions, may occur. Serious hypersensitivity reactions occurred in less than 1% of patients

Please see additional Important Safety Information  
throughout and full Prescribing Information.

**VORAXAZE®**  
(glucarpidase)  
1000 units/vial for intravenous injection

## Leucovorin may not be enough for patients experiencing delayed MTX clearance<sup>2</sup>

### Leucovorin does not clear MTX from the body<sup>2,3</sup>

- Over-rescue with leucovorin in place of Voraxaze is not recommended, as leucovorin is a storage vitamin and this may have implications for future rounds of HDMTX treatment<sup>4</sup>
- HDMTX treatment failures have been reported in pediatric patients following high doses of leucovorin<sup>4</sup>

AKI, acute kidney injury; HDMTX, high-dose methotrexate; MTX, methotrexate.

\*Results are from a single-arm, open-label study in 22 treatment-evaluable patients with markedly delayed MTX clearance secondary to AKI. The primary endpoint of the study was the proportion of patients achieving an MTX plasma concentration of  $\leq 1$   $\mu\text{M}$  at 15 minutes that was sustained for up to 8 days following the initial injection.<sup>1</sup>



Scroll to See How Voraxaze Clears the MTX Backup

### Important Safety Information, cont.

#### Warnings and Precautions

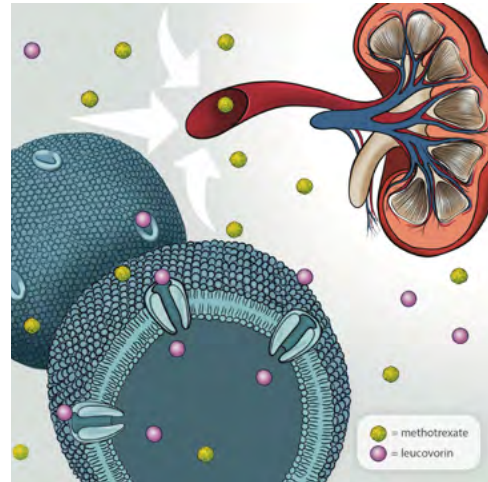
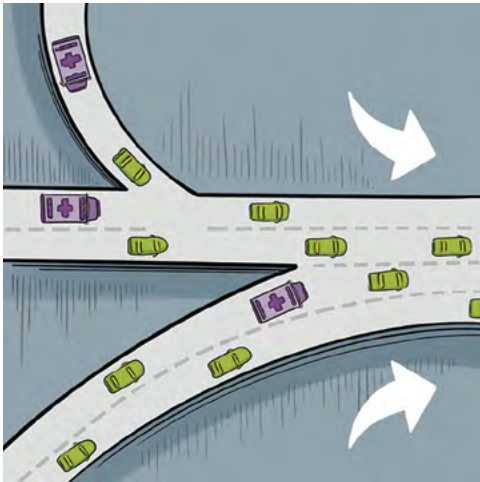
##### Monitoring Methotrexate Concentration/Interference With Assay

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

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1

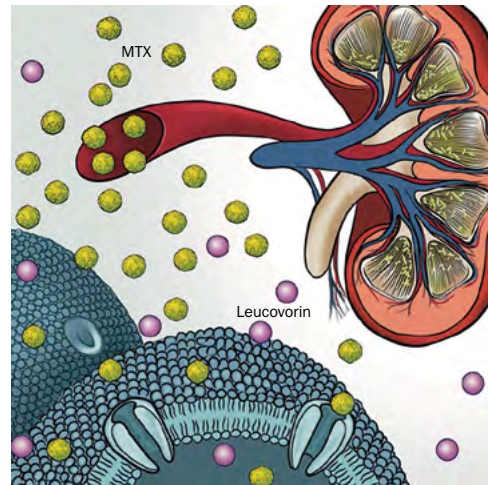
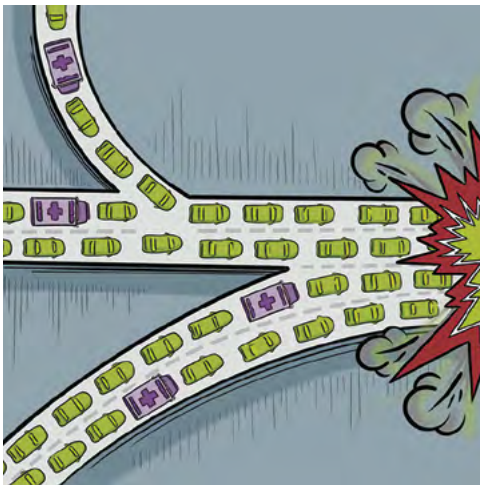
## In normal MTX clearance, MTX circulates throughout the body like cars on a highway



Traffic remains predictable and unobstructed, allowing MTX to flow smoothly to the kidneys for removal from the body.<sup>5</sup> Leucovorin, administered 24-42 hours after MTX, effectively provides aid to the cells.<sup>4</sup>

2

## But in the setting of acute kidney injury, the road becomes too congested for normal MTX clearance to occur



Crystallization of MTX in the renal tubules results in acute kidney injury, which is akin to a traffic jam leading to dangerously elevated levels of MTX in the circulation.<sup>2,5</sup>

AKI, acute kidney injury; MTX, methotrexate.

|                                                                                                                               |                                                                                                                                           |                                                                                                                                         |                                                                                                                                 |                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
|  <b>Methotrexate</b><br>Chemotherapy agent |  <b>Leucovorin</b><br>Intracellular MTX-reducing agent |  <b>Voraxaze</b><br>Extracellular MTX-reducing agent |  <b>DAMPA</b><br>Inactive metabolite of MTX |  <b>Glutamate</b><br>Inactive metabolite of MTX |
|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|

### Important Safety Information, cont.

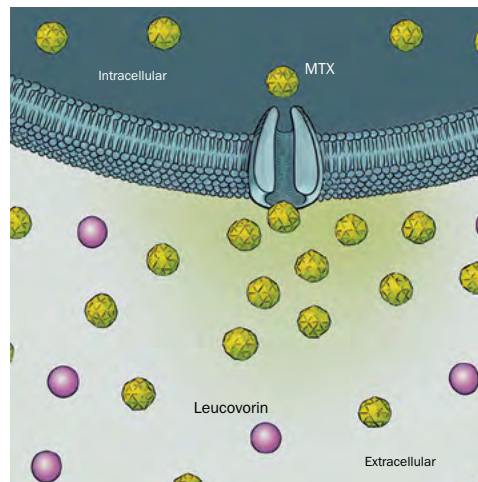
#### Adverse Reactions

- In clinical trials, the most common related adverse events (occurring in >1% of patients) were paresthesia, flushing, nausea and/or vomiting, hypotension and headache

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3

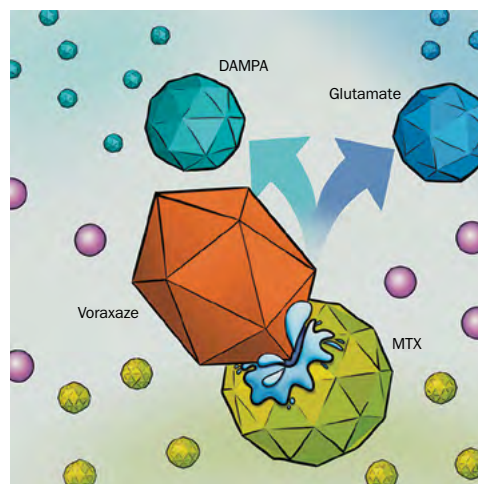
**Prolonged MTX exposure is a clinical hurdle that can lead to potentially irreversible, life-threatening systemic toxicity and organ damage<sup>2,4,5</sup>**



With MTX crowding the entrance to the cell, leucovorin is kept from delivering cell-saving aid.<sup>4</sup> And, if MTX idles for too long in the body, it can lead to life-threatening toxic effects such as mucositis, myelosuppression, and nephrotoxicity.<sup>2,7</sup>

4

**Voraxaze clears  $\geq 97\%$  of the heavily congested traffic with an alternate route<sup>1</sup>**



Voraxaze arrives on the scene, quickly breaking down MTX into nontoxic components, DAMPA and glutamate, and rerouting them through a nonrenal path of elimination.<sup>1,2</sup>

DAMPA, 2,4-diamino-N10-methylpteroic acid; MTX, methotrexate.



## Important Safety Information, cont.

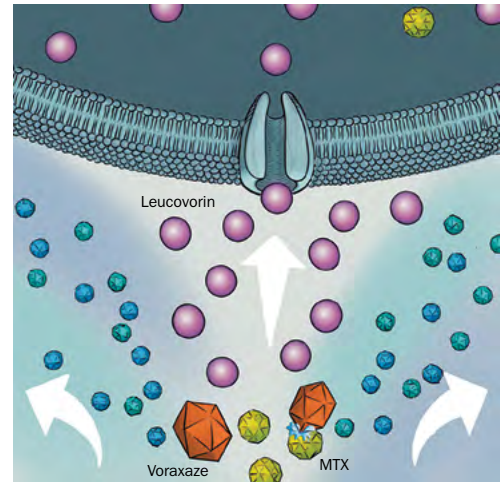
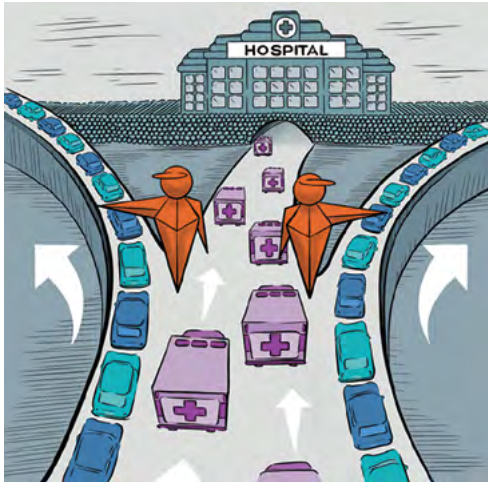
### Drug Interactions

- Voraxaze® can decrease leucovorin concentration, which may decrease the effect of leucovorin rescue unless leucovorin is dosed as recommended, and may also reduce the concentrations other folate analogs or folate analog metabolic inhibitors

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## With the roadway cleared by Voraxaze...

Leucovorin can resume its work in the cells<sup>1,2</sup>



Leucovorin completes its journey to deliver life-saving aid within the cell and the kidneys can begin recovering.<sup>2,4</sup>

## In the face of delayed MTX clearance and AKI, act early and administer Voraxaze<sup>4</sup>

- HDMTX-induced AKI leads to delayed MTX clearance, resulting in **prolonged, elevated plasma MTX concentrations**<sup>2,5</sup>
- **Leucovorin is less effective** in the presence of high MTX concentrations<sup>4</sup>
- Voraxaze lowers plasma MTX levels by **≥97% in 15 minutes** with sustained reduction for up to 8 days<sup>1</sup>

**MTXPK.org\* can help anticipate the hurdle of delayed MTX clearance<sup>8</sup>**

**VISIT [MTXPK.ORG](https://www.mtxpk.org)**

\*The MTXPK.org tool is validated in adult and pediatric patients based on over 40,000 MTX concentrations in 1315 patients.<sup>8</sup>  
AKI, acute kidney injury; HDMTX, high-dose methotrexate; MTX, methotrexate.

 **Methotrexate**  
Chemotherapy agent

 **Leucovorin**  
Intracellular MTX-reducing agent

 **Voraxaze**  
Extracellular MTX-reducing agent

 **DAMPA**  
Inactive metabolite of MTX

 **Glutamate**  
Inactive metabolite of MTX

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# CLEAR THE HURDLE OF DELAYED METHOTREXATE CLEARANCE DUE TO ACUTE KIDNEY INJURY WITH VORAXAZE<sup>1</sup>

- ✓ Administer Voraxaze within 48 to 60 hours of HDMTX infusion start in appropriate patients, based on clinical experience and published guidance<sup>4,\*</sup>
- ✓ Real-world evidence supports the use of Voraxaze in patients with HDMTX-induced AKI<sup>9</sup>
- ✓ MTXPK.org can be used to help determine when Voraxaze is indicated for your patient<sup>1,8</sup>
- ✓ Patients have been successfully rechallenged with HDMTX following Voraxaze treatment<sup>10,11</sup>
- ✓ Expert consensus stocking guidelines and the ISMP recommend that hospitals providing emergency care should stock 5 vials of Voraxaze<sup>1,12,13</sup>

To order Voraxaze, call 1-855-786-7292. To learn more, visit [Voraxaze.com](https://www.voraxaze.com).

[Full Prescribing  
Information](#)

[Learn more about the  
efficacy of Voraxaze](#)

\*Timing should be individualized.  
AKI, acute kidney injury; HDMTX, high-dose methotrexate; ISMP, Institute for Safe Medication Practices.

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**References:** 1. Voraxaze [prescribing information]. BTG International, Inc.; 2019. 2. Howard SC, et al. *Oncologist*. 2016;21(12):1471-1482. 3. Fusilev® [prescribing information]. Acrotech Biopharma LLC; 2020. 4. Ramsey LB, et al. *Oncologist*. 2018;23(1):52-61. 5. Widemann BC, et al. *Oncologist*. 2006;11(6):694-703. 6. Widemann BC, et al. *J Clin Oncol*. 2010;28(25):3979-3986. 7. Dasgupta AD, et al. *J Nephrol*. 2023;36(5):1447-1450. 8. Taylor ZL, et al. *Clin Pharmacol Ther*. 2020;108(3):635-643. 9. Gupta S, et al. *Blood*. 2025;145(17):1858-1869. 10. Christensen AM, et al. *Cancer*. 2012;118(17):4321-4330. 11. Truong HL, et al. *JCO Oncol Pract*. 2024;20(6):797-807. 12. Institute for Safe Medication Practices. ISMP Targeted Medication Safety Best Practices for Hospitals. 2022-2023. Accessed March 4, 2025. [https://www.ismp.org/sites/default/files/attachments/2020-02/2020-2021%20TMSBP-%20FINAL\\_1.pdf](https://www.ismp.org/sites/default/files/attachments/2020-02/2020-2021%20TMSBP-%20FINAL_1.pdf) 13. Dart RC, et al. *Ann Emerg Med*. 2018;71(3):314-325.



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