Beyond 48 to 60 hours, life-threatening toxicities and even death may not be preventable. Consensus Guidelines recommend using Voraxaze® within 48 to 60 hours for optimal nonrenal elimination of MTX.[5]

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

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

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

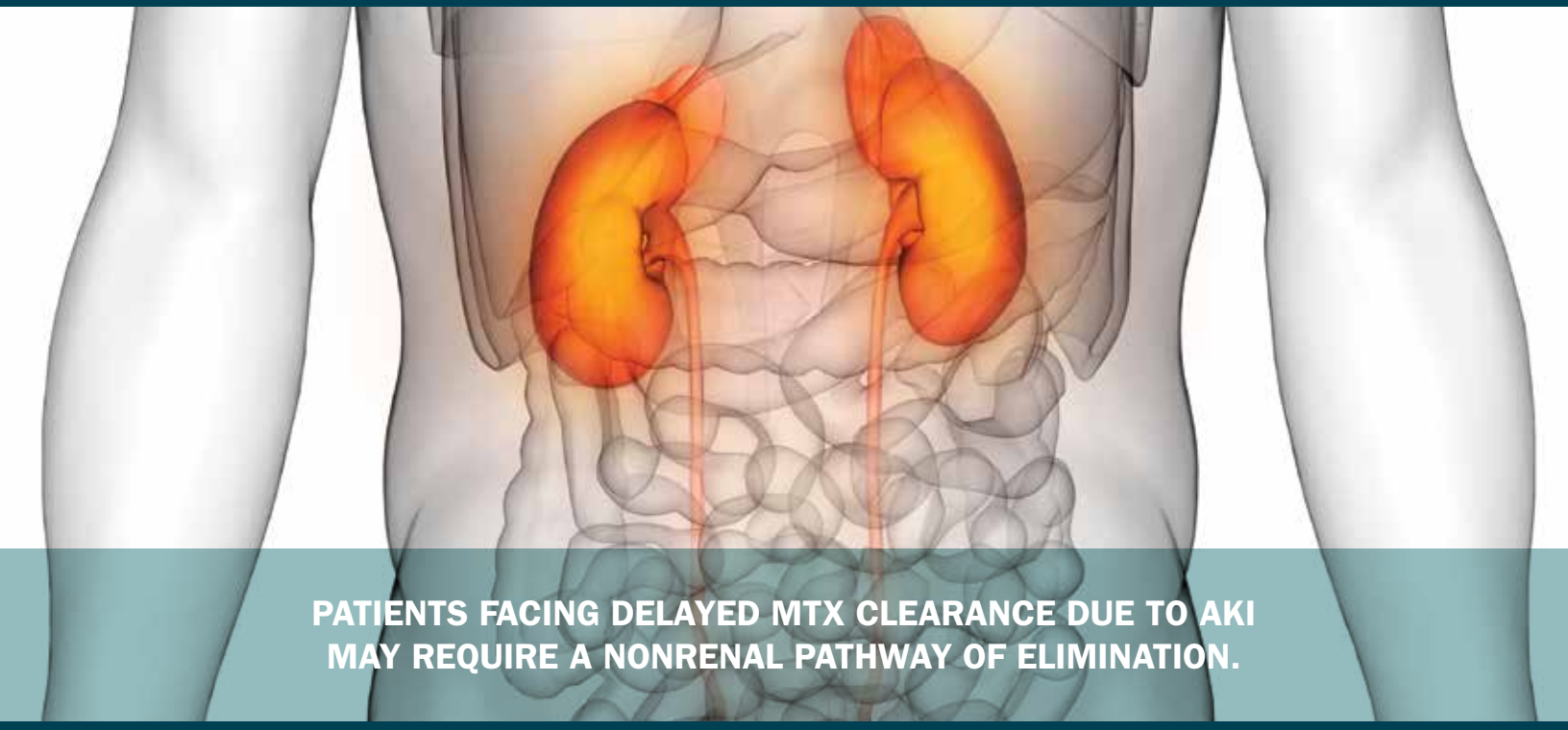
AN ONCOLOGIC EMERGENCY

An estimated 2-12% of patients who receive high-dose methotrexate (HDMTX) chemotherapy will experience delayed clearance due to acute kidney injury (AKI), creating an oncologic emergency.[2,3]

Patients who survive an AKI episode have[6]:

- Double the risk of death
- Triple the risk of end-stage renal disease
- Ten times the risk of developing incident or progressive chronic kidney disease

The rate of cardiovascular events in AKI patients is as high as 22%, and mortality related to cardiovascular events is 33% in patients with AKI.[6]



PATIENTS FACING DELAYED MTX CLEARANCE DUE TO AKI MAY REQUIRE A NONRENAL PATHWAY OF ELIMINATION.

Expert Consensus Stocking Guidelines

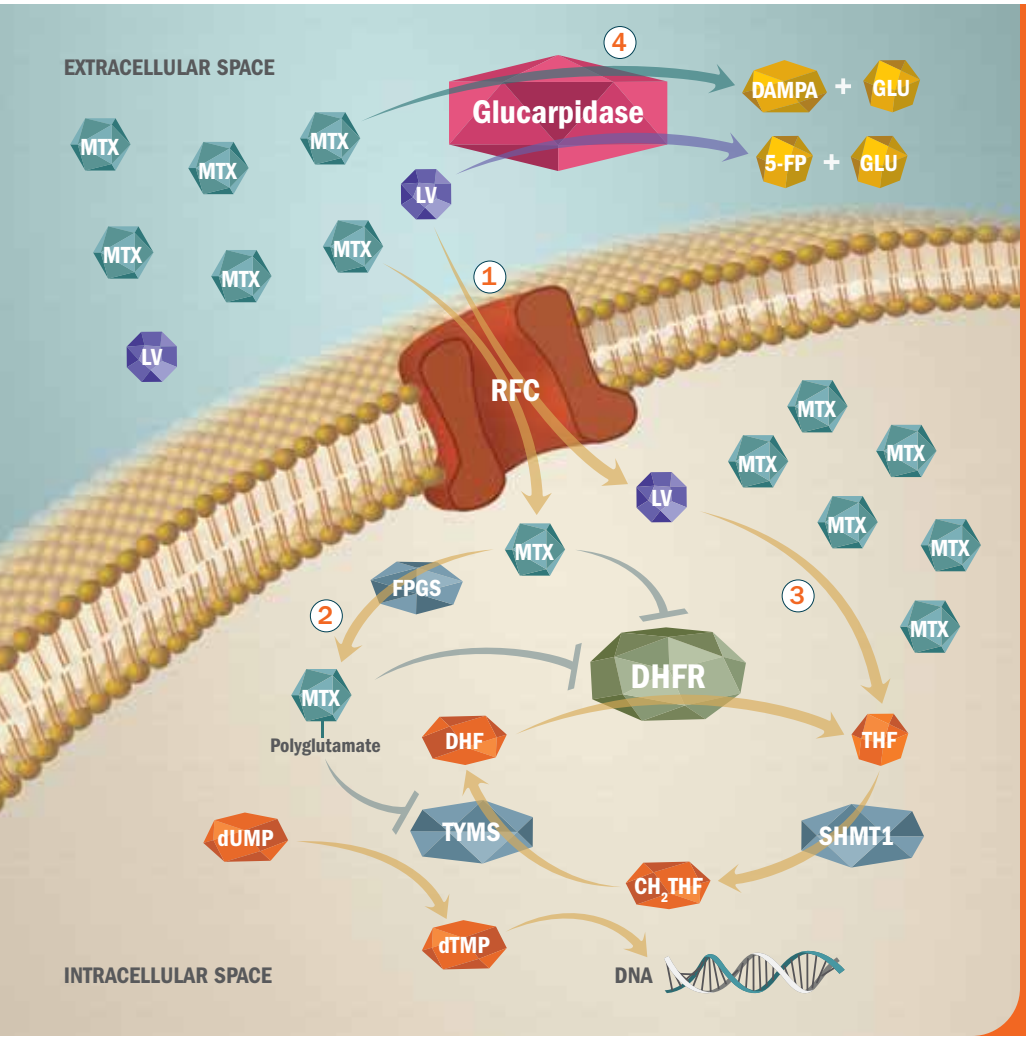
All hospitals that provide emergency care should stock 5 vials of Voraxaze®.[7]

ISMP Best Practices[8]

- The Institute for Safe Medicine Practice (ISMP) recommends all appropriate antidotes should be readily available
- Standardized protocols and/or coupled order should be set in place that permit the emergency administration of all appropriate antidotes used in the facility

Voraxaze® works extracellularly[2]

Voraxaze® and leucovorin work synergistically to reduce methotrexate toxicity: Voraxaze® lowers toxic methotrexate levels in the extracellular compartment while leucovorin counteracts methotrexate intracellularly.



1. Exogenous tetrahydrofolates (LV) must compete with MTX for cellular uptake via the RFC. At higher MTX concentrations, LV may be less effective.[5]
2. MTX is polyglutamated after entering cells and reversibly inhibits DHFR, leading to a significant reduction in DNA and RNA biosynthesis.[5]
3. LV provides **intracellular** rescue following MTX by providing a source of tetrahydrofolate to restore DNA and RNA synthesis despite ongoing inhibition of DHFR via MTX.[5]
4. Voraxaze® eliminates **extracellular** MTX via rapid enzymatic breakdown to nontoxic DAMPA and glutamate. Voraxaze® should be given in conjunction with LV to provide both intracellular and extracellular rescue from unwanted HDMTX toxicity.[5]

5-FU=5-formylpteroate
CH_2THF=5,10-methylenetetrahydrofolate
DAMPA=4-deoxy-4-amino-N10-methylpteroic acid
DHF=dihydrofolate
DHFR=dihydrofolate reductase
dUMP=deoxyuridine monophosphate
dTMP=deoxythymidine monophosphate
FPGS=folylpolyglutamate synthase
GLU=glutamate
LV=leucovorin
MTX=methotrexate
RFC=reduced folate carrier
SHMT1=serine hydroxymethyltransferase-1
THF=tetrahydrofolate
TYMS=thymidylate synthase

Warnings and Precautions

Continuation and Timing of Leucovorin Rescue

- Leucovorin should not be administered within 2 hours before or after Voraxaze® dose because leucovorin is a substrate for Voraxaze®
- For the first 48 hours after Voraxaze®, administer the same leucovorin dose as given prior to Voraxaze®. Beyond 48 hours after Voraxaze®, administer leucovorin based on the measured methotrexate concentration
- Do not discontinue therapy with leucovorin based on the determination of a single methotrexate concentration below the leucovorin treatment threshold
- Therapy with leucovorin should be continued until the methotrexate concentration has been maintained below the leucovorin treatment threshold for a minimum of 3 days
- Continue hydration and alkalinization of the urine as indicated

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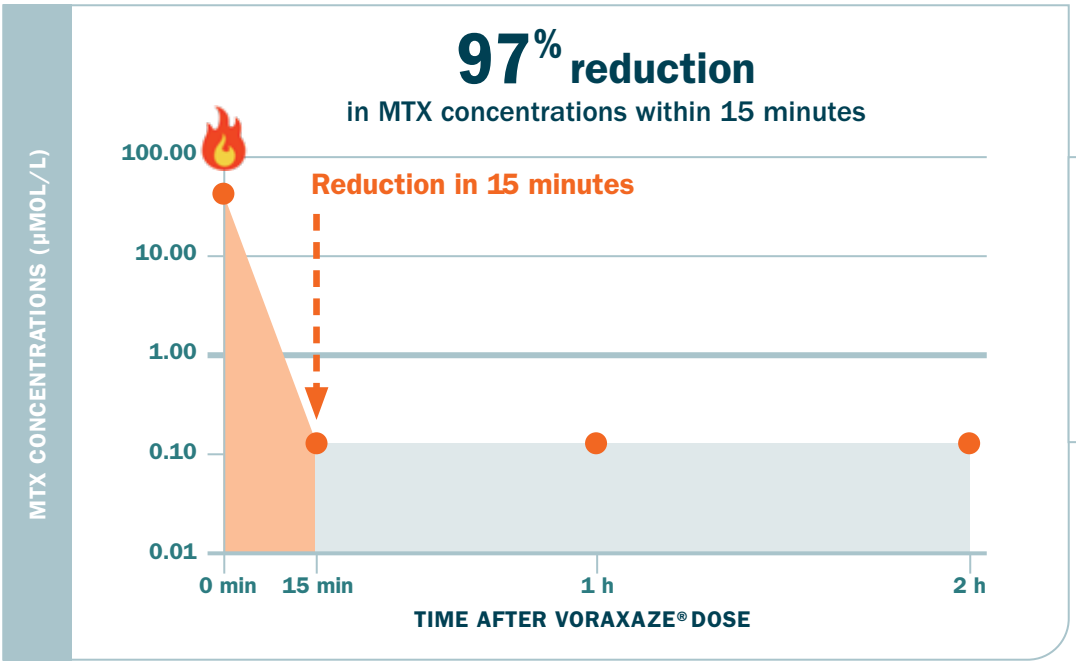
Within 15 minutes

Patients experienced rapid reductions in plasma MTX concentrations[1]



Voraxaze® reduced plasma MTX concentrations by ≥97% within 15 minutes in all 22 treatment-evaluable patients.[1]

At each post-Voraxaze® assessment time point, the median MTX concentration was <0.54 µmol/L, corresponding to a median reduction of ≥97% from pre-Voraxaze® measurements.[9]

Patients sustained reductions in plasma MTX concentrations for up to 8 days[1]

91% of patients taking Voraxaze® (20 of 22) achieved sustained reductions for up to 8 days

45% of patients (10 of 22) achieved rapid and sustained clinically important reduction (RSCIR)

- These 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 RSCIR in plasma MTX concentrations following initial injection
- Of the 12 patients who failed to achieve RSCIR, 5 patients (23%) attained a transient plasma methotrexate concentration of ≤1 µmol/L

Warnings and Precautions (continued)

Serious Hypersensitivity Reactions

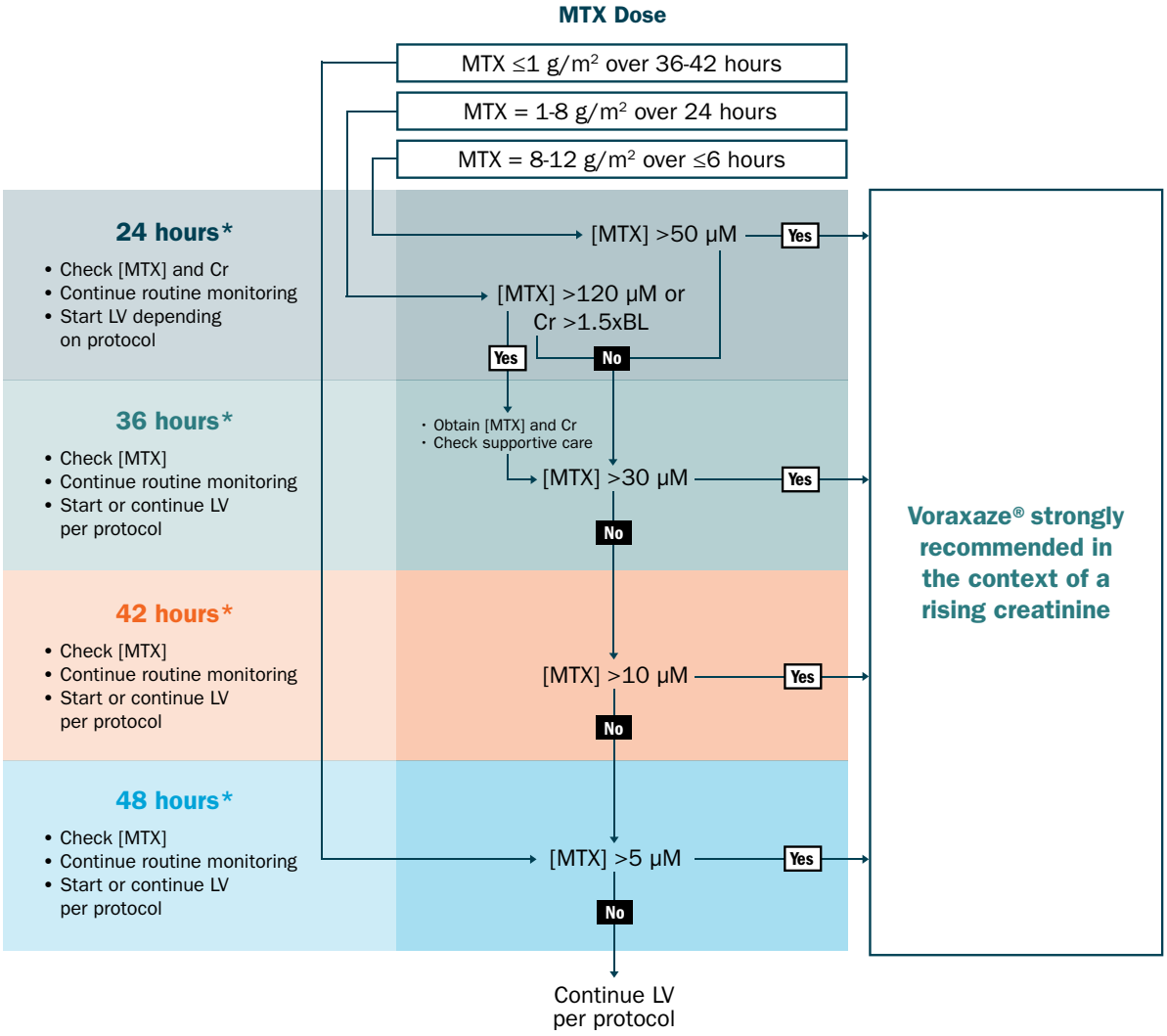
- Serious hypersensitivity reactions, including anaphylactic reactions, may occur. Serious hypersensitivity reactions occurred in less than 1% of patients

Consensus Guidelines recommend early use of Voraxaze®[5]

Consensus Guidelines recommend administration of Voraxaze® at 48 hours following initiation of HDMTX therapy when MTX concentrations are above 5 µM (2.27 µg/mL) and the serum creatinine is elevated relative to the baseline measurement.

Beyond 48 to 60 hours, life-threatening toxicities and even death may not be preventable.

HDMTX Monitoring Guideline and Voraxaze® Treatment Algorithm



*Hours are indicated after infusion start. Provide adequate supportive care (urine pH >7, urine output >2.5 L/m² per day, emesis control).

Abbreviations: BL, baseline; Cr, serum creatinine; HDMTX, high-dose methotrexate; LV, leucovorin (folinic acid, citrovorum factor, 5-methyltetrahydrofolate); MTX, methotrexate; [MTX], plasma methotrexate concentration.

Adverse Reactions

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

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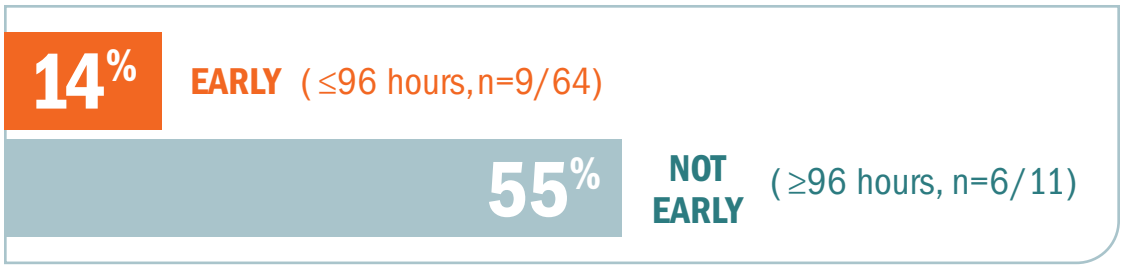
Early administration of Voraxaze® may diminish the risk for serious life-threatening toxicity and even death[3,4]

Incidence of Grade 4 toxicity was significantly lower with early administration of Voraxaze®[3]



- Administration of Voraxaze® ≤96 hours after HDMTX exposure appeared to protect from the development of toxicity
- Grade 4 toxicity developed in only 9/64 (14%) compared to 6/11 (55%) who received Voraxaze® more than 96 hours after starting HDMTX

Incidence of mortality was significantly lower with early administration of Voraxaze®[4]

- Of 476 patients receiving Voraxaze®, death occurred in 22% of patients treated after >4 days of HDMTX compared to 10.9% treated within 2 days of HDMTX
- There are no controlled trials comparing Voraxaze® plus supportive care to supportive care measures alone in patients with toxic plasma MTX concentrations due to impaired renal function; therefore, there are no data regarding the effect of Voraxaze® on survival or toxic death due to MTX. Voraxaze® did not prevent fatal MTX toxicity in 3% of patients in the safety population

Warnings and Precautions (continued)

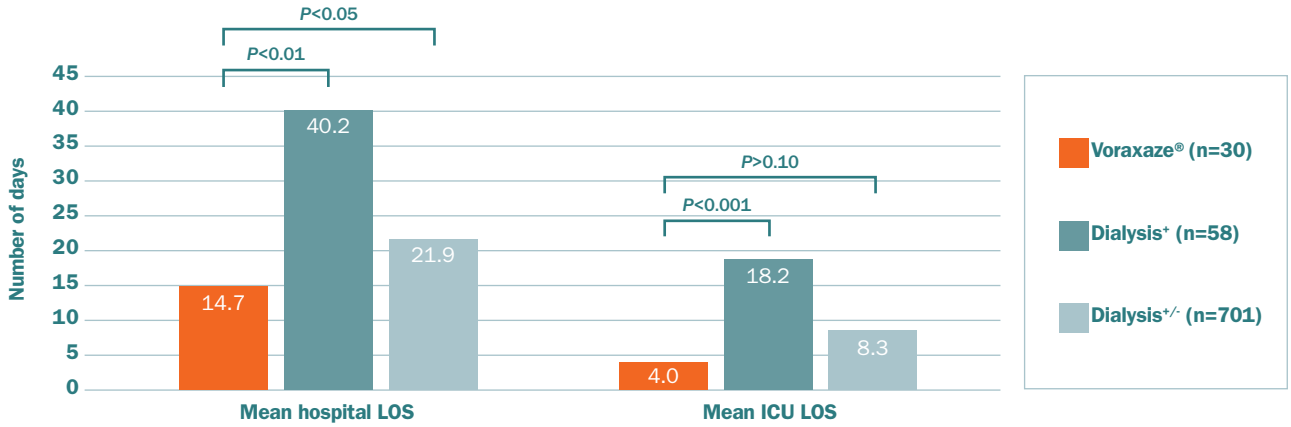
Monitoring Methotrexate Concentration/Interference With Assay

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

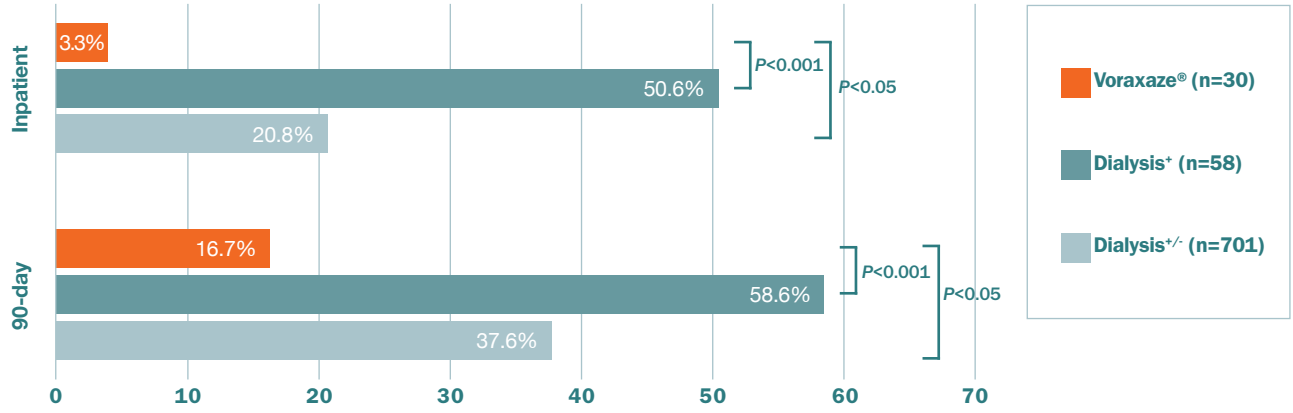
Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Use of Voraxaze® leads to reduced length of stay and reduced mortality rates[6]*

Mean length of stay (LOS) among patients treated with Voraxaze® and the non-Voraxaze® groups



Rates of mortality among patients treated with Voraxaze® and the non-Voraxaze® groups



Early vs late treatment with Voraxaze®[6]

Voraxaze® patients treated within 3 days of admission (n=18) had shorter ICU and hospital LOS compared to Voraxaze® patients treated after 3 days (n=12):

- Length of stay after Voraxaze®: 8.5 days for early cohort vs 14.6 days for late cohort (*P*=0.057)
- Length of ICU stay: 0.8 days for early cohort vs 8.9 days for late cohort (*P*=0.020)

*Utilizing Medicare inpatient claims data between 2010 and 2017, investigators compared outcomes and healthcare resource utilization between patients treated with Voraxaze® (n=30) and patients not treated with Voraxaze® (n=701), all of whom had experienced AKI secondary to inpatient chemotherapy.

Drug Interactions

- In addition to leucovorin (see WARNINGS AND PRECAUTIONS), other potential exogenous substrates of Voraxaze® may include reduced folates and folate antimetabolites

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PUT OUT THE FIRE OF HDMTX TOXICITY
BEFORE IT'S TOO LATE

Consensus Guidelines recommend using Voraxaze® at 48 hours from the start of MTX infusion when MTX concentrations are above 5 µM[5]

In the face of delayed MTX clearance and acute kidney injury, act early and consider Voraxaze®

- 97% reduction in plasma MTX concentrations within 15 minutes[1]
- Clinically important sustained reductions of plasma MTX concentrations for up to 8 days[1]
- Significantly lower rates of Grade 4 toxicity and mortality[4]

Use of Voraxaze® leads to reduced length of stay and reduced mortality rates

- Shorter mean hospital and ICU length of stay[6]
- Lower inpatient and 90-day mortality rates[6]

Included in NCCN Guidelines for[10]:

- Diffuse large B-cell lymphoma
- Burkitt lymphoma
- Adult acute lymphoblastic leukemia (ALL)
- Pediatric ALL
- Primary CNS lymphoma
- Osteosarcoma

The patient you treat today may not clear HDMTX like the patient you saw yesterday. When facing delayed MTX clearance, trust Voraxaze® for rapid and sustained reductions.

www.Voraxaze.com

Warnings and Precautions

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References: 1. Voraxaze® [prescribing information]. BTG International Inc.; August 2019. **2.** Howard SC, McCormick J, Pui CH, et al. Preventing and managing toxicities of high-dose methotrexate. *Oncologist.* 2016;21(12):1471-1482. **3.** Widemann BC, Balis FM, Kim A, et al. Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome. *J Clin Oncol.* 2010;28(25):3979-3986. **4.** 2013 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT). *Clin Toxicol.* 2013;51(7):575-724. **5.** Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guidelines for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. *Oncologist.* 2018;23(1):52-61. **6.** Demiralp B, Koenig L, Kala J, et al. Length of stay, mortality, and readmissions among Medicare cancer patients treated with glucarpidase and conventional care: a retrospective study. *Clinicoecon Outcomes Res.* 2019;11:129-144. **7.** Dart RC, Goldfrank LR, Erstad BL, et al. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. *Ann Emerg Med.* 2018;71(3):314-325. **8.** Institute for Safe Medication Practices. 2018-2019 Targeted medication safety best practices for hospitals. https://www.ismp.org/sites/default/files/attachments/2017-12/TMSBP-for-Hospitalsv2.pdf. Accessed July 24, 2019. **9.** Widemann BC, Schwartz S, Jayaprakash N, et al. Efficacy of glucarpidase (carboxypeptidase G2) in patients with acute kidney injury after high-dose methotrexate therapy. *Pharmacotherapy.* 2014;34(5):427-439. **10.** National Comprehensive Cancer Network. NCCN Guidelines®. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed July 24, 2019.

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US-VRX-1900058 September 2019

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