Medical Information Request: ZUSDURI™ (mitomycin) for intravesical solution and Lab Abnormalities

Thank you for your question regarding ZUSDURI and lab abnormalities reported in the ENVISION clinical trial (NCT05243550).

ZUSDURI™ is indicated for the treatment of adult patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC).[1]

Background:

The reverse thermal properties of ZUSDURI allow for local administration of mitomycin as a liquid under chilled conditions, with subsequent conversion to a semisolid gel depot following instillation into the bladder. Following instillation into the bladder, ZUSDURI forms a semisolid gel which dissolves in the urine. ZUSDURI contains mitomycin which is a violet to blue color and is excreted unchanged in the urine. During clinical studies, patients reported visible purple gel in urine for up to 24 hours (median 5 hours) after instillation. The systemic exposure of mitomycin following instillation of ZUSDURI 75 mg (56 mL) was evaluated pre-instillation and hourly for up to 6 hours post-instillation in 6 patients. Mitomycin mean (range) maximum concentration (Cmax) was 2.3 ng/mL (0.2 to 8.9 ng/mL), which is < 1% of the expected Cmax after intravenous administration.[1-5]

Clinical Trial Design:

ENVISION is a Phase 3, single-arm, multinational study evaluating the efficacy and safety of ZUSDURI (UGN-102) as a primary chemoablative therapy in 240 patients with LG-IR-NMIBC across 56 sites in the United States and Europe.[4]

The primary outcome measure of the trial was Complete Response Rate (CRR) at 3 months. Secondary endpoints are Duration of Response (DOR; up to 63 months), Durable Complete Response (DCR), Disease Free Survival (DFS) and Safety/tolerability of intravesical instillations in patients with LG-IR-NMIBC.

- Patients enrolled in ENVISION were eligible to receive six once-weekly intravesical instillations of ZUSDURI.
- The ZUSDURI admixture for intravesical instillations contains 75 mg mitomycin in 56 mL admixture
- All patients returned to the clinic approximately 3 months after the first instillation for determination of response to treatment. Assessment of response was based on visual observation (white light cystoscopy), histopathology of any remaining or new lesions by central pathology lab (if applicable), and interpretation of urine cytology by central pathology lab.
- Patients confirmed to have a complete response (CR) at the 3-month Visit, defined as having no detectable disease (NDD) in the bladder, entered the Follow-up Period of the study. Patients confirmed to have a non-complete response (NCR) underwent Investigator designated standard of care (SOC) treatment of remaining lesions and then entered the Follow-up Period of the study.
- During the Follow-up Period, patients returned to the clinic every 3 months for up to 24 months (i.e., 27 months after the first instillation) for evaluation of response. Patients who remain disease free at the 27-month Visit will continue to return to the clinic every 6 months for up to 36 months (i.e., 63 months after the first instillation) or until disease recurrence, disease progression, death, or the study is closed by the Sponsor, whichever occurs first.
- Patients confirmed to have a disease recurrence during the Follow-up Period or a disease progression at the 3-month Visit or during the Follow-up Period will undergo Investigator designated SOC treatment and have a separate End of Study (EOS) Visit performed. The timing of the EOS Visit will be approximately 3 months after SOC treatment of disease recurrence or progression.

Safety:

Table 1 summarizes adverse reactions in ENVISION.[1] In Phase 3 ENVISION, 240 patients were analyzed for safety:

- The most common (≥10%) adverse reactions, including laboratory abnormalities, that occurred in patients treated with ZUSDURI were increased creatinine, increased potassium, dysuria, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, increased eosinophils, decreased lymphocytes, urinary tract infection, decreased neutrophils, and hematuria.

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- Serious adverse reactions occurred in 12% of patients who received ZUSDURI, including urinary retention (0.8%) and urethral stenosis (0.4%). A fatal adverse reaction of cardiac failure occurred in 1 (0.4%) patient receiving ZUSDURI.
    - Three patient deaths were reported in the safety analysis set; investigators assessed these were not related to study treatment. There was one listing of death due to unknown reason in a patient with medical history of hypertension, myocardial ischemia, and chronic bronchitis. There was one listing of death due to pneumonia in a patient with medical history of hypertension, coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease. There was one listing of death due to cardiac failure in a patient with medical history of aortic valve disease and cardiac failure.[5]
- Dosage interruption of ZUSDURI due to adverse reactions occurred in 10% of patients. Adverse reactions (≥ 2%) which required dosage interruption were urinary tract infection (2.5%) and dysuria (2.5%).
- Permanent discontinuation of ZUSDURI due to an adverse reaction occurred in 2.9% of patients, including 1.7% who discontinued due to a renal or urinary disorder.

Table 1: Adverse Reactions (≥ 10% All Grades*)
in Patients Who Received ZUSDURI in ENVISION[1]

Adverse Reaction	ZUSDURI N=240	
	All Grades (%)	Grade 3 or 4‡ (%)
Renal and urinary disorders		
Dysuria	23	0.4
Hematuria	10	0
Infections and infestations		
Urinary tract infection†	12	0.8

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
†Includes multiple related terms
‡Only includes Grade 3 adverse reactions

Table 2 summarizes changes from baseline in laboratory parameters relative to the normal range in ENVISION.[1] Clinical laboratory results reported included hematology and chemistry. These analyses should be interpreted with caution, because changes can reflect laboratory values that are only slightly outside of normal range. [4,5]

- Laboratory monitoring is at the clinical discretion of each healthcare professional; the label does not specifically list laboratory monitoring language. According to the label:
    - Monitor patients with moderate renal impairment (eGFR 30 to < 60 mL/min) for increased adverse reactions.[1]
    - Verify pregnancy status in females of reproductive potential prior to initiating ZUSDURI.[1]
- Events classified as bone marrow suppression occurred in 1.7% of patients and consisted of the individual Treatment Emergent Adverse Events (TEAEs) anemia (0.8%), leukopenia (0.4%), neutrophil count decreased (0.4%) and thrombocytopenia (0.4%). One patient (0.4%) had an event that was considered treatment-related [moderate neutrophil count decreased to (0.83×10^9/L)]; this occurred for a brief time period (Study Days 8 to 14) despite continued administration of all planned instillations.[4,5]
    - TEAEs in this category were of mild or moderate severity except for one patient who had severe anemia (not related to treatment or procedure) that started on Study Day 8 and lasted for 104 days. There were no treatment-related severe TEAE's reported in this category.
    - For patients with at least 1 TEAE classified as bone marrow suppression (1.7%), median time to onset of the first event was 8.0 days after starting treatment, and the median duration was 57.5 days.
    - No events in this category led to discontinuation of UGN-102 or to study discontinuation.

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- Creatinine increase from baseline may be expected because many patients presented with mild-moderate renal impairment at baseline consistent with the NMIBC population, and fluctuations in renal function may be expected given frequent, weekly lab assessments.[4,5]
    - Avoid use of ZUSDURI in patients with severe renal impairment (eGFR <30mL/min). A higher incidence of hematuria and urinary tract infections was observed in patients with moderate renal impairment (eGFR 30 to <60 mL/min). Monitor patients with moderate renal impairment for increased adverse reactions. No dosage adjustments are recommended in patients with mild (eGFR 60 to <90 mL/min) or moderate renal impairment.[1]
    - The three patients with reported creatinine increase to Grade 3 (> 3 to 6 x ULN)[5]:
        - One patient had a medical history of pyelonephritis and chronic kidney disease, and at screening Day 1 presented with elevated BUN, eGFR ≤ 34 mL/min, and creatinine Grade 2. Throughout the study, the patient reported a UTI and three events of creatinine increase that resolved, two of which required hospitalization. The patient received all six doses of ZUSDURI and subsequently withdrew consent for the study on Day 100. Investigators considered these events as not related to study treatment.
        - One patient had a medical history of diabetic nephropathy and was on insulin at enrollment, and at screening Day 1 presented with elevated BUN and eGFR 22 mL/min. Creatinine remained at Grade 2 up to Day 96 and worsened to Grade 3 on Day 189. No TEAE's were reported.
        - One patient reported no history of renal disease. BUN, eGFR, and creatinine levels were within normal ranges through six instillations of ZUSDURI. Creatinine increased to Grade 2 concurrent with low eGFR on Day 93, and worsened to Grade 3 concurrent with high BUN and low eGFR on Day 189. No subsequent values were available. No TEAE's were reported.
    - One patient reported TEAE of acute kidney injury, urinary retention, and cystitis on Day 25 (all three related to study treatment and not procedure), and hyponatremia and bladder spasm on Day 30 (not related to study treatment or procedure), and discontinued after 4 instillations.[5]
    - **Table 3** details patients with Creatinine > 194 umol/L (> 2.19 mg/dL) or eGFR ≤ 30, which was the defined potentially clinically significant lab value in safety analysis.[5]
        - 8 patients reported Creatinine > 194 umol/L, and 3 patients reported GFR ≤ 30 only.

Table 2: Laboratory Abnormalities (≥ 10% All Grades*) That Worsened From Baseline in Patients Who Received ZUSDURI in ENVISION[1]

Laboratory Abnormality	ZUSDURI† N=240	
	All Grades (%)	Grade 3 or 4‡ (%)
Hematology		
Hemoglobin Decreased	17	0.8
Eosinophils Increased	15	0
Lymphocytes Decreased	14	0.4
Neutrophils Decreased	10	0.4
Chemistry		
Creatinine Increased	29	1.3
Potassium Increased	26	2.2
Aspartate Aminotransferase (AST) Increased	15	0.4
Alanine Aminotransferase (ALT) Increased	15	0.4

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
†The denominator used to calculate the rate varied from 227 to 238 based on the number of patients with a baseline value and at least one post-treatment value
‡Only includes Grade 3 laboratory abnormalities

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Table 3: Patients Reporting Creatinine > 194 umol/L or eGFR ≤ 30 only[5]

Parameter	Lab Values	
	Baseline Value	Worst Value
Patients reporting Creatinine > 194 umol/L		
Patient 1	180	210
Patient 2	169	604
Patient 3	130	372
Patient 4	68	214
Patient 5	175	202
Patient 6	150	222
Patient 7	110	238
Patient 8	171	201
Patients reporting eGFR ≤ 30 only		
Patient 9	66	23
Patient 10	39	28
Patient 11	25	23

Please refer to the Full Prescribing Information for ZUSDURI here.

ZUSDURI IMPORTANT SAFETY INFORMATION:

Contraindications

ZUSDURI is contraindicated in patients with perforation of the bladder or in patients with prior hypersensitivity reactions to mitomycin or any component of the product.

Warnings and Precautions

Risks in Patients with Perforated Bladder

ZUSDURI may lead to systemic exposure to mitomycin and severe adverse reactions if administered to patients with a perforated bladder or to those in whom the integrity of the bladder mucosa has been compromised. Evaluate the bladder before the intravesical instillation of ZUSDURI and do not administer to patients with a perforated bladder or mucosal compromise until bladder integrity has been restored.

Embryo-Fetal Toxicity

Based on findings in animals and mechanism of action, ZUSDURI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with ZUSDURI and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZUSDURI and for 3 months following the last dose.

Adverse Reactions

Common Adverse Reactions

The most common (≥10%) adverse reactions, including laboratory abnormalities, that occurred in patients treated with ZUSDURI were increased creatinine, increased potassium, dysuria, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, increased eosinophils, decreased lymphocytes, urinary tract infection, decreased neutrophils, and hematuria.

Additional Adverse Reactions Information

Clinically relevant adverse reactions occurring in <10% of patients who received ZUSDURI included increased urinary frequency, fatigue, urinary incontinence, urinary retention, urethral stenosis, genital pain, urinary urgency, genital edema, genital pruritus, genital rash, urethritis, acute kidney injury, balanoposthitis, and nocturia.

Use in Specific Populations

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Lactation

Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ZUSDURI and for 1 week following the last dose.

Preparation and Administration Information

ZUSDURI is to be administered by intravesical instillation only. Do not administer ZUSDURI by pyelocalyceal instillation or by any other route.

ZUSDURI must be prepared and administered by a healthcare provider. To ensure proper dosing, it is important to follow the preparation instructions found in the ZUSDURI Instructions for Pharmacy and administration instructions found in the ZUSDURI Instructions for Administration.

ZUSDURI may discolor urine to a violet to blue color following the instillation procedure. Advise patients for at least 24 hours post-instillation to avoid urine contact with skin, to void urine sitting on a toilet, and to flush the toilet several times after use. Advise patients to wash hands, perineum or glans with soap and water after each instillation procedure.

ZUSDURI is a hazardous drug. Follow applicable special handling and disposal procedures.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit http://www.fda.gov/medwatch or call 1-800-FDA-1088. You may also report side effects to UroGen Pharma at 1-855-987-6436.

Please see accompanying Full Prescribing Information, Instructions for Pharmacy and Instructions for Administration.

References:

1. ZUSDURI™ (mitomycin) for intravesical solution. Prescribing Information. UroGen Pharma; 2025.
2. ZUSDURI™ (mitomycin) for intravesical solution. Instructions for Pharmacy (IFP)
3. ZUSDURI™ (mitomycin) for intravesical solution. Instructions for Administration (IFA)
4. Prasad SM, Shishkov D, Mihaylov NV, et al. Primary chemoablation of recurrent low-grade intermediate-risk nonmuscle-invasive bladder cancer with UGN-102: A single-arm, open-label phase 3 trial (ENVISION). *J Urol.* 2025;213(2):205-16.
5. Data on file. UroGen Pharma.

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