Medical Information Request: JELMYTO® (mitomycin) for pyelocalyceal solution.

Thank you for your question regarding maintenance treatment with JELMYTO.

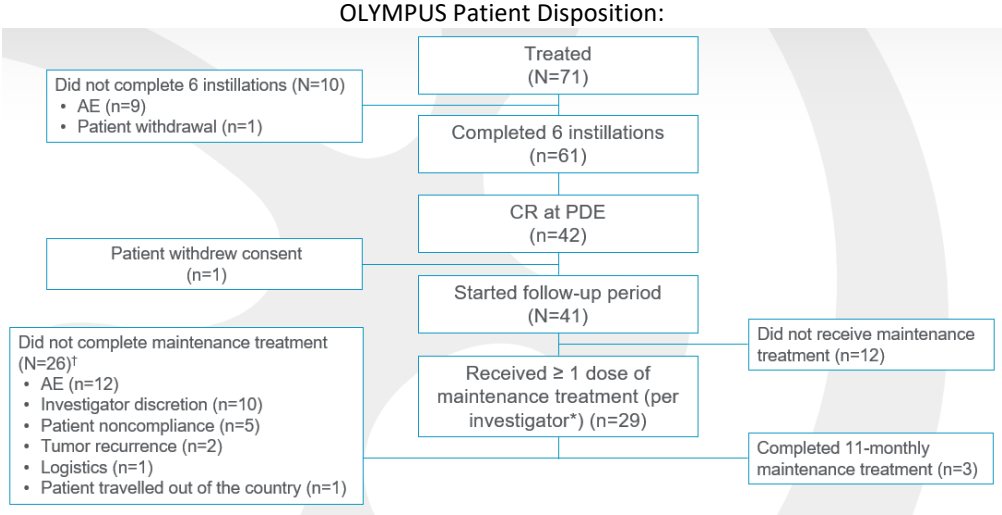
JELMYTO is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC). JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

As per the Prescribing Information, JELMYTO is instilled once weekly for six weeks for induction treatment. **For patients determined to have a complete response 3 months after JELMYTO initiation (post-induction), JELMYTO instillations may be administered once a month for a maximum of 11 additional instillations.**

The results of the Phase 3, prospective, multicenter, open-label, single-arm OLYMPUS trial led to the approval of JELMYTO as a chemoablative agent for adult patients with LG-UTUC in April 2020. In the OLYMPUS trial, all patients received JELMYTO (4 mg/mL mitomycin) via ureteral catheter despite antegrade administration being allowed. Patients were treated with 6 once weekly instillations. **Patients who achieved or were determined to have complete response (CR) after the initial induction period were allowed to proceed to the follow-up period with an option for monthly JELMTYO maintenance up to 11 doses.**

- In the trial, 42 patients achieved a complete response at the primary disease evaluation which took place 4-6 weeks after the completion of induction (at ~3 months).
- After 1 patient withdrew consent, 41 out of 42 patients entered the follow-up period.
- **During the follow-up period, 29 out of 41 patients received at least one dose of maintenance therapy.**
- **Three patients completed 11 monthly maintenance instillations.**

OLYMPUS Patient Disposition:



In the OLYMPUS Trial Final Report published by **Matin et al.**, authors reported that of the 41 patients who had complete response to induction therapy with UGN-101 at the Primary Disease Evaluation visit (PDE) at 3 months, 23 (56%) remained in complete response after 12 months.

- **12 patients received no maintenance treatment, and 29 patients received ≥ 1 maintenance instillation (median 6, range 1 to 11).**
- There were differences in the incidences of individual adverse events (AEs) between the 29 patients who received 1 maintenance treatment and the 42 patients who did not receive any maintenance treatment (comprising 12 patients who were complete responders at the PDE visit but did not receive maintenance and 30 patients who were not complete responders at the PDE visit and were therefore ineligible for maintenance treatment).
- Ureteric stenosis, the most frequently reported treatment emergent adverse event (TEAE) from the urinary disorders organ class, and occurred in 19/29 patients (66%) who received 7 instillations of JELMYTO

400 Alexander Park Drive, 4th Floor, Princeton, NJ 08540 | 646-768-9780

(ie 1 maintenance instillation) compared with 12/42 patients (29%) who received 6 instillations of JELMYTO.

- Although no statistical analyses were performed, TEAEs of urinary tract infection, flank pain, nausea, dysuria, abdominal pain and vomiting occurred in a higher percentage of patients who received 1 maintenance instillation.
- Authors concluded there was no clear association between durability of response and maintenance treatment with 6/12 patients in the no maintenance cohort (50%) and 17/29 patients in the maintenance cohort (59%) maintaining complete response.
- Limitations of this analysis include variability in maintenance treatment across the cohort of patients as well as difficultly to differentiate between relationship of AEs to study drug and relationship to study procedure, particularly in the case of renal and urinary TEAEs.

The following information presented is from an independent retrospective review along with sub-analyses from the same cohort. These are independent publications, and no funding was provided by UroGen Pharma. Due to the retrospective nature, limitations exist including (but are not limited to) lack of centralized pathology review, short follow up time, variable definitions for clinically significant ureteral stenosis, heterogeneity in administration techniques, follow up assessments, and prior treatment.

In November 2022, **Woldu et al.** published "Early experience with UGN-101 for the treatment of upper tract urothelial cancer – A multicenter evaluation of practice patterns and outcomes." This is the first and largest review of Jelmyto's post-approval utilization. This was an independent, retrospective review of JELMYTO cases from 15 high volume academic and community centers throughout the country and represents a heterogeneous and real-world setting. Median follow up was 6.7 months.
There were a total of 136 renal units treated with UGN-101 from a total of 132 patients, with 4 patients receiving bilateral UGN-101 treatment.

- Amongst patients with absence of disease on initial endoscopic evaluation following UGN-101 induction, **maintenance was utilized in 27% (n = 16).**
- **The most common regimen was monthly maintenance (n = 14), while other regimens included 3 weekly doses at 3 months (n = 1), and 1 dose every 2 months (n = 1).**

Woldu et al. (2025) published a long-term follow up from the Woldu et al. (2023) study, titled "Durability of response of UGN-101: Longitudinal follow up of multicenter study" in *Urologic Oncology*. This presents three-year, longitudinal outcomes in the 56 renal units who presented no evidence of disease following JELMYTO induction.

Endpoints included recurrence-free survival (RFS); progression data; and Kaplan Meier survival analysis stratified by relevant clinical features, including HG vs LG disease. Median (IQR) follow-up was 23.5 (17.4-28.0) months. Per the authors, the administration of maintenance treatment did appear to be associated with significantly better RFS, however, it should be acknowledged that only 15 renal units received maintenance therapy; further study is required to determine the value of maintenance treatments.

- 15 renal units received maintenance therapy and there was statistically significant improvement in the risk of recurrence in those which received maintenance therapy (log rank P=0.021)
    - **RFS stratified by use of maintenance therapy showed estimated RFS of 24.6 months (95% CI 21.2-27.9) for cases with no maintenance and 34.3 months (95% CI 32.4-36.1) for cases with maintenance (Log rank P=0.02)**
    - One case of recurrence in those who received maintenance therapy
    - Half of the cases which did not receive maintenance therapy recurred within 2 years
    - This analysis is notable for a high censoring rate in the cohort which received maintenance and the number at risk is low.
- Overall, 65% of renal units were recurrence-free.
- Median time to recurrence was not reached, but mean survival estimate was 29.0 months.
- The authors did not mention safety data.

400 Alexander Park Drive, 4th Floor, Princeton, NJ 08540 | 646-768-9780

Please refer to the package insert and www.jelmyto.com for the full Prescribing Information.

IMPORTANT SAFETY INFORMATION

Contraindications
JELMYTO® (mitomycin) for pyelocalyceal solution is contraindicated in patients with perforation of the bladder or upper urinary tract.

Warnings and Precautions
Ureteric Obstruction
Ureteric obstruction, including ureteral stenosis and hydronephrosis, occurred in patients receiving JELMYTO. Monitor patients for signs and symptoms of ureteric obstruction, including flank pain, and fever, and for changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures. Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

Bone Marrow Suppression
The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

Embryo-Fetal Toxicity
Based on findings in animals and mechanism of action, JELMYTO 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 JELMYTO and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose.

Adverse Reactions
Common Adverse Reactions
The most common adverse reactions in ≥ 20% of patients treated with JELMYTO were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, nausea, abdominal pain, fatigue, dysuria, and vomiting.

Additional Adverse Reactions Information
Selected clinically relevant adverse reactions in < 10% and > 2% of patients who received JELMYTO include urinary tract inflammation, bladder spasm, urosepsis, hypersensitivity, and instillation site pain.

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

Preparation and Administration Information
JELMYTO is for pyelocalyceal use only and not for intravenous use, topical use, or oral administration. JELMYTO must be prepared and administered by a healthcare provider. To ensure proper dosing, it is important to follow the preparation instructions found in the JELMYTO Instructions for Pharmacy and administration instructions found in the JELMYTO Instructions for Administration.

400 Alexander Park Drive, 4th Floor, Princeton, NJ 08540 | 646-768-9780

JELMYTO may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use.

JELMYTO 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.

References:

1. JELMYTO® (mitomycin) for pyelocalyceal solution. Prescribing Information 2024. UroGen Pharma, Princeton, New Jersey.
2. Kleinmann et al. *The Lancet. Oncology* vol. 21,6 (2020): 776-785. https://pubmed.ncbi.nlm.nih.gov/32631491/
3. Matin et al. *J Urol*. 2022; 207(4):779-788. https://pubmed.ncbi.nlm.nih.gov/34915741/
4. Woldu et al. *Urologic oncology*, Nov. 2022. https://pubmed.ncbi.nlm.nih.gov/36424224/
5. Rose et. al. *Eur Urol Focus* (2023). https://pubmed.ncbi.nlm.nih.gov/37059620/
6. Woldu SL, Igel D, Johnson B, et al. Durability of response of UGN-101: Longitudinal follow up of multicenter study. Urol Oncol. 2025 Jan 20:S1078-1439(24)01059-7. doi: 10.1016/j.urolonc.2024.12.279. Epub ahead of print. https://pubmed.ncbi.nlm.nih.gov/39837708/

400 Alexander Park Drive, 4th Floor, Princeton, NJ 08540 | 646-768-9780