CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211728Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 6, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 211728
Product Name and Strength:	Jelmyto (mitomycin) for pyelocalyceal solution
Applicant/Sponsor Name:	UroGen Pharma, Inc. (UroGen)
OSE RCM #:	2019-310-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling, Instructions for Pharmacy (IFP), and Instructions for Administration (IFA) received on April 1, 2020 for Jelmyto. Division of Oncology 1 (DO1) requested that we review the revised container labels, carton labeling, IFP, and IFA for Jelmyto (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors study report and label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Little, C. Human Factors Study Report and Label and Labeling Review for Jelmyto (NDA 211728). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 02. RCM No.: 2019-310 and 2019-1508-1.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COLLEEN L LITTLE
04/06/2020 11:44:58 AM

LOLITA G WHITE
04/06/2020 12:05:18 PM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 2, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 211728
Product Type:	Single Ingredient Product
Drug Constituent Name and Strength	Jelmyto (mitomycin) for pyelocalyceal solution
Rx or OTC:	Rx
Applicant/Sponsor Name:	UroGen Pharma, Inc. (UroGen)
Submission Date:	July 11, 2019, December 13, 2019, January 3, 2020, March 2, 2020, and March 25, 2020
OSE RCM #:	2019-310 and 2019-1508-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report for the preparation process, the HF validation study report for the administration process, and labels and labeling submitted under NDA 211728 for Jelmyto (mitomycin) for pyelocalyceal solution. This is a single- ingredient product that is intended to treat low-grade Upper Tract Urothelial Cancer (UTUC).

1.1. PRODUCT DESCRIPTION

Jelmyto must be reconstituted and administered by a healthcare provider. Jelmyto is supplied in a kit that contains two 40 mg vials of mitomycin for solution (drug component) and one 20 mL vial of Sterile Hydrogel (non-active component). Sterile Hydrogel is a reverse thermal vehicle for reconstitution that allows for the retention of the drug component in the target organ, resulting in prolonged exposure of the tumor cells. Jelmyto is liquid at lower temperatures and converts into a semisolid gel at body temperature. This temperature-dependent viscosity characteristic requires Jelmyto to be prepared under chilled conditions using the UroGen Pharma Chilling Block, which is provided separately from the proposed Jelmyto kit. Jelmyto is highly viscous, even in a chilled state, therefore; healthcare providers must use a Uroject12 Syringe Lever (provided separately) to instill Jelmyto into the patient for administration.

1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On June 1, 2015, we participated in a Pre-IND Type B meeting for IND 121922.[a] We advised the Applicant to discuss the implication of the proposed formulation and its preparation for administration on potential medical errors, labeling, and approvability issues with the Agency.

On January 27, 2016, we participated in a Pre-IND Type B meeting for IND 121922 to discuss and gain agreement on the adequacy of the proposed development plan to support the marketing application.[b] We requested the Applicant validate the proposed preparation

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[a] Balcazar, P. Meeting Minutes for PIND 121922. Silver Spring (MD): FDA, CDER, OHOP, DOP1 (US); 2015 JUN 12. Available from: https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af803990f4&_afrRedirect=4018273414517887

[b] Banerjee, A. Meeting Minutes for PIND 121922. Silver Spring (MD): FDA, CDER, OPQ, OND (US); 2016 FEB 22. Available from: https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af803d3069&_afrRedirect=4019122367418987

instructions in a HF validation study. We encouraged the Applicant to submit their HF validation study protocol for Agency's review and feedback prior to commencing the study and their HF study results at the time of NDA submission.

On March 12, 2018, the Applicant submitted their HF validation study protocol to evaluate the proposed Instructions for Pharmacy (IFP) under IND 121922. On May 8, 2018, we participated in a Pre-NDA Type B meeting to discuss the Applicant's HF engineering plan to evaluate the IFP.[c] We acknowledged the March 12, 2018 Human Factors Protocol submission and notified the Applicant that we will provide written comments during the completion of our review. Upon completion of our review of the HF validation protocol, we provided recommendations to the Applicant.[d] We included a recommendation to revise the HF validation study protocol to evaluate the mixing task D11 in the IFP during the simulated use scenario to reflect real world performance.

Subsequently, on October 5, 2018, the Applicant submitted a revised HF validation study protocol under IND 121922. We noted that the Applicant did not implement all of our recommendations, including the recommendation relating to IFP task D11. On November 8, 2018, during the course of our review of the revised HF validation study protocol, the Applicant informed the Agency via email of the completion of their HF validation study. While we acknowledged the completion of the HF validation study, our review of the Applicant's revisions determined that the HF validation study protocol could be further improved. Thus, we provided additional recommendations to the Applicant relating to the HF validation study protocol, which again included a recommendation relating to the assessment of IFP task D11 via simulated tasks.[e]

On June 10, 2019, we participated in a Pre-NDA Type B teleconference with the Applicant to discuss the Applicant's proposed changes to the packaging configuration, which included inclusion of all of the single-use devices required for the preparation and administration of Jelmyto (e.g., vial adaptors, syringe adaptors, etc.).[f] Given the proposed changes to the user

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[c] Banerjee, A. Meeting Minutes for PIND 121922. Silver Spring (MD): FDA, CDER, OPQ, OND (US); 2018 JUN 06.
https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af8049ed58&_afrRedirect=4020307463904327

[d] Little, C. Human Factors Protocol Review for Mitogel (IND 121922). Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2018 JUN 08. RCM No.: 2018-718.

[e] Little, C. Human Factors Protocol Review for Mitogel (IND 121922). Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2018 OCT 05. RCM No.: 2018-718-1.

[f] Rizvi, F. Meeting Minutes for UGN-101 IND 121922. Silver Spring (MD): FDA, CDER, OHOP, DOP1 (US); 2019 JUL 02.

interface, we requested the Applicant to clarify if they intended to repeat their HF validation studies to support the safe and effective use of the newly proposed packaging configuration. We determined that we agreed with the Applicant that is was not necessary to repeat HF validation testing with the newly proposed packaging configuration because the newly proposed packaging configuration did not impact any critical tasks as compared to the packaging configuration evaluated in the HF validation study.

On July 11, 2019, the Applicant submitted the IFP and IFU (Instructions for Use) HF validation study reports under NDA 211728. During the course of our review of the IFP HF validation study report, we noted the absence of simulated use data that evaluates the duration and swirling intervals for IFP task D11. Thus, on October 9, 2019,[g] we issued an IR (Information Request) to request the aforementioned simulated use data.

In response to our October 9, 2019 IR, the Applicant stated that only the placement of the mitomycin vials in the Chilling Block and the swirling technique for IFP task D11 were assessed during the simulated use scenario.[h] Thus, we determined that the results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient. On December 3, 2019, we issued an IR to convey our concerns with the identified use errors, close calls and use difficulties observed in the HF validation study relating to steps under IFP sections D: Mix the admixture, E: Prepare admixture vial, and F: Dispense Admixture Vial." Additionally, we found the Applicant's plan to implement mitigations without performing an additional HF validation study unacceptable, so we included recommendations for the Applicant to implement prior to conducting their additional HF validation study.[i]

Upon review of the Applicant's response to our December 3, 2019 IR[j], we were unable to determine if the Applicant planned only evaluate IFP step D11 in the additional HF

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https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af80502471&_afrRedirect=4034276078870948

[g] Rizvi, F. FDA Communication: NDA 211728 Information Request. Silver Spring (MD): FDA, CDER, OND, DO1; 2019 OCT 09.

[h] UroGen Pharma, Inc. Quality Information Amendment for Jelmyto NDA 211728. 21 OCT 19. Available from: \\cdsesub1\evsprod\nda211728\0009\m1\us\1-11-1-response-to-ir-hf-device.pdf

[i] Rizvi, F. FDA Communication: NDA 211728 Information Request. Silver Spring (MD): FDA, CDER, OND, DO1; 2019 DEC 10. https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af8052c700&_afrRedirect=4036384295034625

[j] UroGen Pharma, Inc. Quality Information Amendment for Jelmyto NDA 211728. 2019 DEC 13. Available from: \\cdsesub1\evsprod\nda211728\0014\m1\us\1-11-1-human-factors-req-response.pdf

validation study. We also noted that the Applicant did not plan to implement all recommendations included in our December 3, 2019 IR. Thus, on January 6, 2020, we held a teleconference[k] with the Applicant to discuss our concerns regarding the Applicant's response to our December 3, 2019 IR during which Applicant agreed to evaluate all IFP tasks in the additional HF validation study.

Thus, on March 2, 2020, the Applicant submitted the results of their additional IFP HF study which evaluated all IFP tasks and validated our recommendations provided in the December 3, 2019 IR.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

[k] Rizvi, F. Teleconference Meeting Agenda for NDA 211728. Silver Spring (MD): FDA, CDER, OND, DO1; 2020 JAN 30. https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af8053c9ba&_afrRedirect=4038568881780560

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The Applicant conducted one HF validation study and one supplemental HF study that evaluated if the intended user could safely and effectively prepare the Jelmyto solution in the intended use environment. These HF validation studies evaluated IFP tasks and included 12 pharmacy technicians and 3 pharmacists. The participants completed a simulated-use scenario and knowledge-assessment tasks.

We note that the Applicant conducted an additional mixing robustness study on several aspects of the preparation process that are included in the IFP. Based on these data, we note several success criteria in the additional IFP HF validation study were updated. For example, the success criteria for IFP step C8 ,"The participant pushed the plungers back and forth at least 25 times" was changed to "The participant pushed the plungers back and forth at least (b)(4) times." We sought input from the Office of Pharmaceutical Quality (OPQ) to help determine the acceptability of the results from the additional mixing robustness study. OPQ stated that the results from the additional mixing robustness study appear reasonable and support the proposed preparation process. Additionally, we note that the Applicant did not revise the IFP based on the results of the additional mixing robustness study and we find this appropriate. Thus, we aligned with the Applicant's updated success criteria in the additional HF validation study.

In addition to the IFP HF validation studies, the Applicant conducted a HF validation study that evaluated if the intended user could safely and effectively instill Jelmyto solution in the intended use environment. This HF validation study evaluated IFU tasks and included 15 urologists and 15 assist dyads (i.e., non-sterile nurses and sterile nurses or technicians). The assist dyad participants completed a simulated-use scenario during which they prepared a syringe of Jelmyto that would be later instilled by the urologist participants. The urologist participants completed the simulated instillation of the prepared Jelmyto dose into a mannikin. After completing their respective tasks, both user groups (i.e., urologists and assist dyads) completed knowledge assessment tasks.

3.2 RESULTS AND ANALYSES

Table 2 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 2: Discussion of Identified Issues and Recommendations		
	Discussion of Identified Issue	DMEPA's Analysis and Recommendations

1.	In simulation of the IFU task to chill the admixture vial for at least 10 minutes, there were 3 use difficulties. In the report, 3 assist dyad participants did not sufficiently chill the vial. For the 10 minute chilling time knowledge assessment task, 1 assist dyad participant did not have awareness of the minimum required chilling time of 10 minutes. • A (b)(6) chilled the vial for 10 minutes but did not ensure that all sides of the vial were sufficiently covered by ice so they were unable to withdraw the admixture. • A (b)(6) initially attempted to withdraw the admixture without chilling the vial and was only able to withdraw about 8 mL. • A (b)(6) only chilled the vial for about 1 minute before attempting to withdraw the admixture. • A (b)(6) stated the admixture vial should be kept in the ice bath initially for at least two or three minutes. The subjective data and the Applicant's root cause analysis indicated that: • The IFU lacks any indication that suggests how much of the vial should be immersed in the ice bath. • The admixture container label does not provide the volume of admixture. • The only indication of the minimum chilling time is in the IFU and is not included on the	Based on the Applicant's use-related risk analysis, if the admixture vial is placed in the ice bath for more than 75 minutes, there is a risk of compromised efficacy. We acknowledge that the use difficulties observed in the IFU HF validation study resulted in participants removing the admixture vial from the ice bath before the minimum 10 minute period (not after 75 minutes). However, we are concerned that misinterpretation of this task may lead to delays in therapy that exceed 75 minutes if users do not chill the admixture for the recommended time and experience difficulties administering the solidified solution. For example, participant A (b)(6) indicated there was not enough in the vial for a full dose and they would call the pharmacy for more. Participant A (b)(6) stated, "…because the extra step [we took], the catheter is inserted already, its increasing risk for infection and surgical time." Our review of the IFU determined that step C1 and the corresponding graphical images can be improved. Additionally, our review of container labels finds the minimum chilling time (i.e., at least 10 minutes) should be included on the admixture container label. Thus, we provide recommendations #5, 7, and 10 in Table 4 to address this concern. We have determined that these changes can be implemented without additional validation testing to be submitted for review.

	admixture vial label. However, the Applicant did not implement additional mitigations and/or user interface changes to further address these issues.	

3.4. LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

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Table 3: Identified Issues and Recommendations for Division of Oncology 1			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information- Section 2			
1.	The "Stability of Reconstituted JELMYTO" section includes post-reconstitution storage information and identifying characteristics of the dosage forms.	We are concerned that users may overlook the post-reconstitution storage information because it appears with the identifying characteristics of the dosage forms and the corresponding temperature ranges which may lead to confusion and deteriorated drug error.	1. Consider relocating the identifying characteristics of the dosage forms (e.g., semisolid gel) and to section 3. 2. Consider revising the title of this subsection to "Storage of Reconstituted JELMYTO" for clarity.
2.	The storage statements for reconstituted Jelmyto across labels and labeling are not consistent.	We are concerned that inconsistency between the storage statements may lead to confusion and deteriorated drug error.	We recommend advising the Applicant to ensure the storage statement is consistent across PI, container labels, carton labeling, IFU, and IFP. We defer to OPQ to determine the final post-constitution storage statement for this product. We recommend a storage statement similar to

			"Store reconstituted Jelmyto at controlled room temperature, 20°C to 25°C (68°F to 77°F) for up to 8 hours or chilled at -3°C to 5°C (27°F to 41°F) for (b) (4). Protect reconstituted Jelmyto from light.
Full Prescribing Information -Section 16			
3.	Jelmyto kit storage statements across labels and labeling are not consistent.	We are concerned that inconsistency between the storage statements may lead to confusion and deteriorated drug error.	1. We recommend advising the Applicant to ensure the storage statement is consistent across PI, container labels, carton labeling, IFU, and IFP. We defer to OPQ to determine the final storage statement for the kit. 2. We recommend revising "Store JELMYTO…" to "Store the JELMYTO kit…" for clarity.
4.	Section 16 does not include the NDC numbers for the mitomycin and sterile hydrogel; however, the NDC numbers for are provided on the proposed container labels.	We are concerned that inconsistent information throughout labels and labeling may lead to confusion.	We recommend providing the NDC number for each component of the kit (i.e., mitomycin and sterile hydrogel).

Table 4: Identified Issues and Recommendations for UroGen (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Pharmacy (IFP)			
1.	As proposed, the IFP includes 2 notes under step A1 and step B2 that refers users to the Chilling Block IFU for additional information.	Given the number of notes within your IFU, we are concerned that users may become desensitized to all notes, potentially overlooking the most critical notes.	Consider removing "Note: Please refer to the Chilling Block Instructions for Use for additional information" under step B2.
2.	Step F1 instructs users to (b) (4)	The word "(b) (4)" is unclear. We are concerned this lack of clarity may lead to misinterpretation and degraded drug medication error.	Revise step F1 to read "Write the Discard after date and time on the admixture label and apply to the prepared Jelmyto vial.
3.	The note under step F1 states, "(b) (4) 8 hours from the completion of the preparation at room temperature". However, the term "(b) (4)" is not present on the admixture container label.	We are concerned the use of terminology which is not clear or consistent may lead to confusion.	Revise the note under step F1 to read "The Discard after date and time is 8 hours from… room temperature".
4.	The graphical images in the "Supplies Needed" section includes undefined acronyms (i.e., "PI" and "IFU").	Undefined acronyms may cause confusion if healthcare practitioners (HCP) cannot easily find the meaning of the acronym.	Define the acronyms "PI" and "IFU". We recommend including the acronyms in the bulleted list under the "…carton containing" section of the IFP. For example, • 1 Jelmyto Prescribing Information (PI) • 1 Jelmyto Instructions for Pharmacy (IFP) • 1 Jelmyto Instructions for Use (IFU)
Instructions for Use (IFU)			

5.	In section C. Chill the Jelmyto, (b) (4)	Based on the use errors in your validation study, your root cause analysis indicated that the IFU does not clearly suggest how much of the vial should be immersed in the ice bath. For example, participant A (b) (6) chilled the vial for 10 minutes but did not ensure that all sides of the vial were sufficiently covered by ice so they were unable to withdraw the admixture.	Revise (b) (4) section C to depict the admixture vial fully immersed in the ice bath. Consider an image similar to the image provided in the "Frequently Asked Questions" section of the IFU (see below). 
6.	The IFU states that a Jelmyto Administration Kit will be sent from the pharmacy to the treatment room. However, the Instructions for Pharmacy states that only the admixture vial and IFU are transported to the treatment facility.	We are concerned that inconsistent information throughout labels and labeling may lead to confusion and result in delay of therapy.	1. Clarify if the "Jelmyto Administration Kit" is a component of your intend-to-market user interface. 2. If treatment facilities are expected to provide the Tevadaptor adaptor, leurlock syringe, and ureteral catheter; relocate these items to appear in the "Ancillary Supplies" section of the IFU.
7.	Step C1 states, "…in the ice bath for at least10minutes…" and includes the graphic 	Based on the use errors in your validation study, we are concerned users may misinterpret the minimum amount of time the vial should remain in the ice bath. For example, (b) (6) only chilled the vial for about 1 minute before	1. Increase the prominence of the "10 min" graphic. Consider revising the graphic to provide a more realistic representation of a clock. Additionally, consider including the text, "Wait 10 min." to accompany the graphic. 2. Revise the statement to "…at least 10 minutes…" to correct the typographical error.

		attempting to withdraw the admixture. We presume that "least10minutes" is a typographical error. Typographical errors may lead to confusion.	
8.	The presence of the warning statement, (b) (4) under step B1.	Postmarketing reports suggest negative statements (e.g. (b) (4)) may have the opposite of the intended meaning because the word "(b) (4)" can be overlooked and the warning may be misinterpreted as an affirmative action.[l]	Revise the warning statement to a statement similar to "Maximum instillation volume is 15 mL."
9.	The description of the user interface can be improved. For example, step D7 instructs users to press the "clutch" button"; however, the "clutch button" is not identified in the IFU.	Referring users to unidentified components of the user interface may lead to confusion.	Revise the graphical image of the Uroject12 Syringe Lever to identify and label the clutch button.
Admixture Container Label			
10.	The admixture container label does not provide the minimum chilling time for the admixture vial.	Based on the use errors in your validation study, your root cause analysis indicated that the only indication of the minimum chilling time is in the IFU and is not included on the admixture	Revise the statement, (b) (4) to "Jelmyto must be chilled for <u>at least 10 minutes</u> to revert back to liquid form for instillation."

[l] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

		vial label. For example, participant (b) (6) stated the admixture vial should be kept in the ice bath for maybe initially for at least two or three minutes.	

4. CONCLUSION AND RECOMMENDATIONS

We generally find the results of the HF validation studies acceptable. Our evaluation of the of the IFU HF validation study identified use difficulties associated with one of the critical tasks, which is to chill the admixture vial for at least 10 minutes. We are concerned that when users do not chill the admixture for the recommended time, they may experience difficulties administering a semisolid product, which may result in harm to the patient. We have provided recommendations to revise the IFU to improve prominence, clarity and understanding of important information in Table 4. These recommendations are based on our evaluation of the subjective feedback and root cause analyses as well as our expert review of the proposed product user interface. In this particular instance, we have determined that these changes can be implemented without submission of additional HF validation testing data for Agency's review.

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Thus, we have provided additional recommendations in Table 3 for the Division and Table 4 for the Applicant. Our recommendations in Table 4 were previously conveyed to the Applicant (See Appendix E).

4.1 RECOMMENDATIONS FOR UROGEN PHARMA, INC.

Our evaluation of the of the IFU HF validation study identified use difficulties with one of the critical tasks which is to chill the admixture vial for at least 10 minutes. We are concerned that when users do not chill the admixture for the recommended time, they may experience difficulties administering a semisolid product, which may result in harm to the patient. Additionally, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have previously conveyed our recommendations on March 19, 2020 and March 26, 2020.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Jelmyto that UroGen submitted on January 3, 2020.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	alkylating drug
Active Ingredient (Drug or Biologic)	mitomycin
Indication	low-grade Upper Tract Urothelial Cancer (UTUC)
Route of Administration	pyelocalyceal
Dosage Form	for pyelocalyceal solution
Dose and Frequency	The dose of JELMYTO to be instilled is 4 mg per mL, with total instillation volume based on volumetric measurements using pyelography, not to exceed 15 mL (60 mg of mitomycin). Instill JELMYTO once weekly for six weeks. For patients with a complete response 3 months after JELMYTO initiation, JELMYTO instillations may be administered once a month for a maximum of 11 additional instillations.
How Supplied	Each kit contains: • 2 vials of mitomycin powder, 40 mg per vial • 1 vial of sterile hydrogel, 20 mL per vial • 1 admixture label • Prescribing Information • Instructions for Pharmacy • Instructions for Use
Storage	Before reconstitution: Store the Jelmyto kit at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59 °F and 86°F) [see USP Controlled Room Temperature]. Avoid excessive heat over 104°F (40°C). After reconstitution Jelmyto should be instilled immediately. If immediate instillation is not possible, store at [redacted] (b) (4) 20°C to 25°C (68°F to 77°F) for up to 8 hours. Protect from light.

	When ready to instill, chill Jelmyto at -3°C to 5°C (27°F to 41°F) for at least 10 minutes, but no longer than one hour, to revert to liquid form.
Intended Users	pharmacists, pharmacy technicians, urologists, nurses or technicians assist with uteroscopy procedures
Intended Use Environment	pharmacy, endoscopy or cystoscopy suites

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On March 18, 2020, we searched the L:drive and AIMS using the terms, IND 121922 and NDA 211728 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified 3 previous reviews[m,n,o], and we confirmed that our recommendations were implemented or considered.

[m] Little, C. Human Factors Protocol Review for Mitogel (IND 121922). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 08. RCM No.: 2018-718.

[n] Little, C. Human Factors Protocol Review for Mitogel (IND 121922). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 05. RCM No.: 2018-718-1.

[o] Little, C. Human Factors Results Review Memorandum for Jelmyto (NDA 211728) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 03. RCM No.: 2019-1508.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information pertaining to the IFP can be accessible in EDR via:
\\cdsesub1\evsprod\nda211728\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\utuccarcinoma\5354-other-stud-rep\human-factors-ifp\hf-ifp-protocol-valp0002270.pdf

\\cdsesub1\evsprod\nda211728\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\utuccarcinoma\5354-other-stud-rep\human-factors-ifp\hf-ifp-protocol-vt2-101.pdf

The background information pertaining to the IFU can be accessible in EDR via:
\\cdsesub1\evsprod\nda211728\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\utuccarcinoma\5354-other-stud-rep\human-factors-ifu\hf-ifu-protocol-devp0007253.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report evaluating the IFP submitted on July 11, 2019 can be accessible in EDR via:
\\cdsesub1\evsprod\nda211728\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\utuccarcinoma\5354-other-stud-rep\human-factors-ifp\hf-ifp-report-valr0005188.pdf

The HF study results report evaluating the IFU submitted on July 11, 2019 can be accessible in EDR via:

\\cdsesub1\evsprod\nda211728\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\utuccarcinoma\5354-other-stud-rep\human-factors-ifu\hf-ifu-report-valr0007901.pdf

The supplemental HF study evaluating the IFP submitted on March 2, 2020 can be accessible in EDR via:
\\cdsesub1\evsprod\nda211728\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\utuccarcinoma\5354-other-stud-rep\human-factors-ifp\hf-ifp-rpt-supp-vt2-503.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On March 19, 2020, DO1 communicated our container labels and carton labeling recommendations for Jelmyto to the Applicant.

- Our IR and the Applicant's response can be accessible in EDR via:
  \\cdsesub1\evsprod\nda211728\0043\m1\us\1-11-4-response-to-fda-labels.pdf

On March 26, 2020, DO1 communicated our recommendations for the revised container labels and carton labeling and for Jelmyto received on March 25, 2020 to the Applicant.

- Our IR and the Applicant's response can be accessible in EDR via:
  \\cdsesub1\evsprod\nda211728\0044\m1\us\1-11-4-response-container-carton.pdf

On March 26, 2020, DO1 communicated our IFP and IFU recommendations to the Applicant.

- Our IR can be accessible in DARRTS via: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8054fe0f&_afrRedirect=5308939034130274

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[p] along with postmarket medication error data, we reviewed the following revised Jelmyto labels and labeling submitted by UroGen.

- Mitomycin Container label received on March 25, 2020
- Sterile Hydrogel Container label received on March 25, 2020
- Admixture Container label received on March 25, 2020
- Carton labeling received on March 25, 2020
- Instructions for Pharmacy received on March 2, 2019 can be accessible in EDR via: \\cdsesub1\evsprod\nda211728\0034\m1\us\1-14-1-3-proposed-ifp.pdf
- Instructions for Use received on July 11, 2019 can be accessible in EDR via: \\cdsesub1\evsprod\nda211728\0002\m1\us\114-labeling\114a-draft-label\ifu-word.docx
- Prescribing Information (Image not shown) received on January 3, 2020 can be accessible in EDR via: \\cdsesub1\evsprod\nda211728\0018\m1\us\1-14-1-3-draft-label-text.docx

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[p] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Clinical Inspection Summary

Date	3/26/2020
From	Yang-min (Max) Ning, M.D., Ph.D. Kassa Ayalew, M.D., M.P.H. GCPAB/OSI/CDER/FDA
To	Dow-Chung Chi, M.D. Daniel Suzman, M.D. Fatima Rizvi, RPM DO1/OOD/OND/CDER/FDA
NDA#	211728
Applicant	UroGen Pharma Ltd.
Drug	Mitomycin gel
NME (Yes/No)	No
Therapeutic Classification	Chemotherapeutic agent
Proposed Indication	For treatment of low-grade upper tract urothelial cancer
Submission Date	October 18, 2019
Consultation Date	November 15, 2019
Review Priority	Priority
Summary Goal Date	March 31, 2020
Action Goal Date	April 18, 2020
PDUFA Date	April 18, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single-arm trial (Study TC-UT-03) were submitted to the Agency in support of a New Drug Application (NDA) for mitomycin gel for the treatment of patients with low-grade, upper tract urothelial cancer. Three clinical investigators, Dr. Surena Matin (Site 21), Dr. Phillip Pierorazio (Site 11), and Dr. Ahmad Shabsigh (Site 16), were selected for clinical inspection.

The inspections of Drs. Matin and Pierorazio found no significant regulatory deficiencies and the submitted data for the two investigator sites were verified with source records. The clinical data generated by the two sites appear reliable.

The inspection of Dr. Shabsigh verified four subjects enrolled into the study and identified three subjects (Subjects (b) (6), and (b) (6)) whose urine cytology results were questionable for the reported complete response (CR) as per the definition described in the

study protocol. This finding, along with the collected site's source records, was conveyed to the review team in the Week of February 24, 2020. See detailed information regarding this site inspection and communications with the review team and related OSI recommendations in Section III of this summary.

There was no evidence of underreporting of adverse events from the three inspected investigator sites.

II. BACKGROUND

Mitomycin is a chemotherapeutic agent that inhibits the synthesis of deoxyribonucleic acid. Mitomycin gel (or UGN-101 under IND 121922) is a reconstituted preparation of mitomycin with hydrogel. The reconstituted product is proposed to be instilled into the pyelocalyceal system for the treatment of patients with low-grade, upper tract urothelial cancer. To support the new indication, the Applicant submitted clinical data from Study TC-UT-03, titled "A Phase 3 Multicenter Trial Evaluating the Efficacy and Safety of MitoGel (UGN-101) on Ablation of Upper Urinary Tract Urothelial Carcinoma (UTUC)".

Study TC-UT-03 (NCT02793128) was an open-label, single-arm, multicenter trial in subjects with low-grade UTUC. To be eligible for the study, subjects were required to have treatment-naïve or recurrent, low-grade, non-invasive UTUC with at least one measurable papillary tumor of 15 mm or less. In addition, subjects were required to have documented absence of high-grade urothelial carcinoma in the washing urine cytology sampled from the pyelocalyceal system less than 2 months prior to screening. The primary endpoint of this study was the proportion of subjects attaining a Complete Response (CR) at the visit of primary disease evaluation (PDE), which was to be performed 5 weeks (± 1 week) after the last study treatment.

Subjects enrolled in this study were to have mitomycin gel instilled into the pyelocalyceal system once weekly for six weeks. The instillation was required to be performed using the designated Injector Device supplied by the sponsor UroGen. The instillation dose was individualized based on volumetric measurements using pyelography and was limited to 15 mL (60 mg mitomycin) or less.

Following completion of the instillation treatment course, response of low-grade UTUC to mitomycin gel was assessed with a ureteroscopy examination at the PDE visit. Subjects who had no detectable disease (NDD) were considered to have had a CR. To determine NDD for each subject, the study protocol specified that the following requirements had also to be met.

1) "If visual ureteroscopy assessment indicated no remaining tumors, the upper tract urine cytology had to be negative."

2) "If tumors were visible during ureteroscopy examination, all remaining and accessible tumors were biopsied and evaluated by a local and a central pathologist. If the biopsied tumors were not viable upon histopathological evaluation and the cytology was negative, the subject was considered to have attained a CR."
3) "In case where a subject underwent a radical nephroureterectomy for any reason, and the pathological evaluation indicated that no viable tumor(s) remained in the affected kidney (e.g., non-viable lesion), the subject was considered attaining a CR retrospectively."

The protocol stated that tumor response at the PDE visit was to be determined "based on upper tract wash urine cytology followed by visual evaluation using video-ureteroscopy (appearance, number, size, and location of the lesions) and histopathology of remaining lesions". If no lesion was detected via ureteroscopy, but the urine cytology from the upper tract was equivocal (see Figure 1: Method for Determining Complete Response on Page 29 of the study protocol version 6), subjects were to be re-evaluated by urine cytology prior to the next scheduled maintenance treatment (~3 weeks after the original cytology test at the PDE) and prior to the instillation on that day. If the urine cytology was negative, the subject was to be considered attaining a CR. If the repeat urine cytology was equivocal or positive, the subject was to be considered "failure" (non-CR).

For the primary endpoint analysis, local pathology and upper tract urine cytology results were to be used. The cytology and histopathology slides/specimens were also to be sent to the sponsor's designated central pathology laboratory (b) (4) . Results from the central laboratory were intended to provide supportive evidence and/or a sensitivity analysis for this study.

From 01/30/2017 through 05/22/2019 (data cutoff date for the analysis in this NDA), this study enrolled 74 subjects. Eighty percent of subjects were recruited from 22 study sites in the U.S. and 20% from 2 study sites in Israel. Of the enrolled subjects, 71 received study treatment with mitomycin gel. Three enrolled subjects did not receive study treatment due to evidence of high-grade pathology found after their enrollment and/or investigator's decision.

The review division, Division of Oncology 1 (DO1), and Office Scientific Investigation (OSI) selected the above three clinical investigator sites for clinical inspections. Relative to other sites for this study, these three sites had a high number of subjects enrolled. In addition, Sites 11 and 16 were associated with a higher CR rate than the overall CR rate in the reported evaluable population of study subjects. In addition, none of the three clinical investigators had prior FDA clinical inspections.

III. RESULTS

1. **Surena Matin, M.D. (Site 21)**
   1515 Holcombe Blvd.
   Houston, TX 77030

   The clinical investigator was inspected on February 10-13, 2020 as a data audit for Study TC-UT-03. This was the initial FDA inspection of this investigator. The site screened 12 subjects and enrolled 9 of them into the study. As of the data cutoff date, all the enrolled subjects completed the study. Two subjects (Subjects (b) (6)) were reported to have attained CR at the PDE visit.

   Source records were reviewed for all the 6 enrolled subjects and were compared with the Applicant's submitted data listings for the site. The reviewed records included but were not limited to the informed consents, inclusion/exclusion criteria, medical history, computed tomography urography (CTU) or MRI scans performed, volumetric estimation of the pyelocalyceal system, instillation of mitomycin gel, ureteroscopies performed, biopsies for histopathology and urine cytology reports, adverse events and serious adverse events. Documents related to the conduct and oversight of this study at the site, including the study protocol and amendments, Institution Review Broad's (IRB) approvals, signed Form FDA1572s, financial disclosures, training on the study protocol, and sponsor's monitoring, were also reviewed during the inspection.

   The inspection found no significant regulatory deficiencies and verified the reported efficacy and safety data with source records for all the treated subjects. There was no evidence of underreporting of adverse events and protocol violations. At the conclusion of the inspection, no Form FDA 483 was issued to the investigator.

2. **Phillip Pierorazio, M.D. (Site 11)**
   600 N Wolfe Street
   Baltimore, MD 21287

   This clinical investigator was inspected on February 10-14, 2020 as a data audit for Study TC-UT-03. This was the first FDA inspection of Dr. Pierorazio. The investigator site screened 7 subjects and enrolled 6 subjects into the study. As of the data cutoff, two subjects remained on the study, two subjects completed the study, and two subjects were discontinued from the study due to death (Subject (b) (6)) or withdrawal (Subject (b) (6)). Three subjects (Subjects (b) (6)) were reported to have achieved CR at the PDE visit.

   The inspection included a comprehensive review of the subject source binders, regulatory binders, study enrollment, and investigational product (IP) accountability.
   All subject records were reviewed for the consent, eligibility, medical history records, pathology reports, records of protocol-specified procedures, and general protocol adherence. The Applicant's submitted data listings were examined with source data.

The inspection revealed consistency between the reviewed source records and the submitted data listings for this site. All adverse events and serious adverse events appeared to be accurately documented and reported.

The review of source records also identified that some missed laboratory values, as shown in the data listings (e.g., no reports of bilirubin, phosphorous and uric acid levels at different study visits in three subjects), were associated with no tests ordered or performed according to the study protocol. The investigator acknowledged the finding and explained that these tests were not incorporated into the built-in labs of the study institute initially. The staff was re-educated on the importance of collecting all protocol-required labs and had since been more diligent in checking the lab orders. This finding was discussed with the investigator study team at the closeout meeting for the inspection.

No Form FDA-483, Inspectional Observations, was issued to the investigator at the conclusion of the inspection.

3. Ahmad Shabsigh, M.D. (Site 16)
460 W. 10th Avenue
Columbus, OH 43210

This clinical investigator was inspected from February 10 through February 26, 2020, as a data audit for Study TC-UT-03. This was the initial FDA inspection for the investigator. The investigator site enrolled four of the six screened subjects into the study. As of the data cutoff, three subjects remained on the study and subject (Subject (b) (6)) completed the study. At the time of this inspection, all the four subjects completed the study. Three enrolled subjects (Subjects (b) (6)) were reported to have attained a CR at the PDE visit.

The inspection included a comprehensive review of source records and evaluated the accuracy of the Applicant's submitted efficacy and safety data for the site. The reviewed records for this inspection included but were not limited to the informed consent, medical records, eligibility, IRB's approvals, drug accountability, adverse event reporting, and case report forms (CRF).

At the conclusion of the inspection, a Form FDA-483 was issued to the investigator with the following two Observations. Information contained in the Observations is summarized as follows:

1) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation

   Three subjects (Subjects (b) (6)) who had no visual detection of tumor lesions per urethroscopy examination were found to have source cytology results showing that their upper tract wash urine cytology was not unquestionably negative for urothelial carcinoma at the PDE visit. However, these three subjects were reported by the study staff to have a CR at the PDE in their CRF. Detailed

cytology and clinical information regarding this observation and related discrepancies is summarized in the following table.

Subject ID	Date of PDE	Source Upper Tract Urine Cytology Report	Investigator's Clinical Note	Reported Response to Sponsor
(b) (6)	6/8/2018	"Clusters of urothelial cells: the differential diagnosis includes a low-grade urothelial lesion, instrumentation effect, or stones. Clinical correlation is recommended"	"positive urine cytology for low grade disease" in the 7/3/18 office visit note	Complete Response
	6/29/2018	"Rare Atypical Urothelial Cell in A Background of Acute Inflammation, Cannot Exclude Carcinoma"	"inconclusive" in the 7/12/18 progress note	Complete Response
	10/4/2018*	"Urothelial Atypia, Cannot Exclude Low Grade" (carcinoma)	(Not described)	Complete Response
*At the 3-month follow-up visit on 1/10/2019, the urine cytology report showed "suspicious for urothelial carcinoma".				

2) An investigation was not conducted in accordance with the investigational plan

For the above three subjects, the investigator did not repeat the upper tract urine cytology testing per the protocol after the local cytology results at the PDE visit were equivocal.

In addition, the investigator did not report a serious adverse event (SAE) within 24 hours after becoming aware of the event for Subject (b) (6). This subject was hospitalized at an outside facility from (b) (6) 18, at the study facility from (b) (6) and from (b) (6), respectively. For each incident, the investigator assessed the SAE to be possibly related to the study drug.

In the Investigator's written response dated March 17, 2020, he acknowledged the observations and provided his explanations for the discrepancies in determination of a CR for the three listed subjects. He stated that the main purpose of upper tract urine cytology test was to detect residual disease of high-grade urothelial carcinoma (HGUC). If HGUC was not detected in a sample, then that test was considered "negative". The initial cytology results obtained for the three subjects at the PDE visits were deemed negative and not "equivocal" and therefore he did not repeat these tests. The investigator also stated that regarding the cytology result for Subjects (b) (6) 3 and (b) (6), he communicated with the Principal Coordinating Investigator of this study, Dr.

Seth Lerner, and their consensus was that the sample (of each subject) was negative per the protocol. With respect to his clinical notes for the two subjects, as listed in the above table, he explained that his notes served "as a reminder to myself to watch for any changes which may suggest progression to high grade disease" or "a reminder to myself and my team to look closely at the patient's next exam". In addition, he stated "due to detection of no measurable lesion per cystourethroscopy assessment and extensive discussion of local and central cytology results with the sponsor, a determination of "CR" was made for all 3 patients".

Reviewer's Comments: *Determination of a CR using the absence of HGUC in urine cytology at the PDE visit was not described or found in the approved study protocol.*

As specified in the Background of this summary, the protocol stated: "If visual ureteroscopy assessment indicated no remaining tumors, the upper tract urine cytology had to be negative". This statement indicates that both HGUG and low-grade carcinoma should be considered in determination of a CR. This is also reflected by the study CRF, which included HGUG and low-grade urothelial carcinoma in the checklist for the PDE visit. Regarding the three questioned subjects, the upper tract urine cytology results, as listed in the above table, did not clearly show that their urine cytology at the PDE was negative, but rather were questionable or equivocal in that low-grade carcinoma could exist or could not be excluded in the specimens read by local pathologists. See additional Reviewer's Comments below regarding the reported data for these three subjects.

With respect to the delayed reporting of the SAE to the sponsor, the investigator explained that it was caused by his misinterpretations of the protocol's requirements for reporting.

In his written response, the investigator confirmed that all enrolled study subjects came off the study and the study was closed at the site. He provided his corrective and preventive action plans for ongoing trials, and stated that on March 11, 2020, the study team members were retrained to ensure adequate documentation and the SAE reporting guidelines for study protocols. The submitted training records showed the name of attendees and items discussed. Additionally, he stated that mandatory training programs for all research staff are required, including but not limited to "GCP Training" and "Data Collection Training". As a principal investigator, he will continue to provide the required oversight and will ensure that staff follow protocol guidelines.

Reviewer's Comments: *Given that three of the four enrolled subjects at Dr. Shabsigh's site had discrepancies between source records and the submitted primary endpoint data, the DO1 review team was notified of the inspection observations immediately upon feedback from the inspection. Relevant documents including the ureteroscopy and urine cytology reports were conveyed in the Week of 2/24/2020. With the evidence found in these documents as well as the Observations specified in the issued Form FDA 483, we recommended the review team to communicate with the Applicant and clarify whether the three subjects (as listed in the above table) had urine cytology results that*

clearly showed "negative for urothelial carcinoma" to support the reported CRs. OSI also suggested conducting additional analyses as needed to address the issue and/or to accurately reflect the efficacy of mitomycin gel in the intended patient population.

As discussed above, OSI review of the Investigator's written response, received on 3/24/2020, found that the Investigator's stated criteria for defining a CR at the PDE were related to whether high-grade urothelial carcinoma was detected in the upper tract urine cytology besides the requirement of no remaining tumors per ureteroscopy assessment. This is not well consistent with the criteria described in the study protocol (see Reviewer's Comments above), representing a considerable protocol deviation or a change in determination of a CR and/or interpretation of the reported efficacy data. Whether the change in the criteria is clinically relevant and whether the CR data from the three subjects from this study site is acceptable should be prudently assessed by the DO1 review team.

{See appended electronic signature page}

Yang-min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA 211728
Review Division /Deputy Division Director/A Ibrahim
Review Division /Medical Team Leader/D Suzman
Review Division /Project Manager/F Rizvi
Review Division/Medical Officer/DC Chi
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Khin
OSI/DCCE/GCPAB Chief/K Ayalew
OSI/DCCE/GCPAB Reviewer/YM Ning
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 27, 2020

To: Dow-Chung Chi, M.D.
Division of Oncology 1 (DO1)

Fatima Rizvi PharmD, Regulatory Project Manager, DO1

William Pierce, PharmD, Associate Director for Labeling, (DO1)

From: Emily Dvorsky, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for JELMYTO™ (mitomycin) for pyelocalyceal solution

NDA: 211728

In response to DO1 consult request dated October 24, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for JELMYTO™ (mitomycin) for pyelocalyceal solution (Jelmyto).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DO1 (Fatima Rizvi) on March 25, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 25, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 27, 2020
To:	Fatima Rizvi, PharmD Regulatory Project ManagerDivision of Oncology 1 (DO1)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Dvorsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	JELMYTO (mitomycin)
Dosage Form and Route:	For pyelocalyceal solution
Application Type/Number:	NDA 211728
Applicant:	Urogen Pharma Ltd.

1 INTRODUCTION

On October 18, 2019, Urogen Pharma Ltd., submitted for the Agency's review an original New Drug Application (NDA-211728) for JELMYTO (mitomycin) for pyelocalyceal solution, for the proposed indication of use for the treatment of low-grade (LG) upper Tract Urothelial Cancer (UTUC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 1 (DO1) on March 20, 2020 and October 24, 2019, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for JELMYTO (mitomycin) for pyelocalyceal solution.

2 MATERIAL REVIEWED

- Draft JELMYTO (mitomycin) PPI received on October 18, 2019 and received by DMPP and OPDP on March 25, 2020.
- Draft JELMYTO (mitomycin) Prescribing Information (PI) received on October 18, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 25, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI .

Please let us know if you have any questions.

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