CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217424Orig1s000

OTHER REVIEW(S)

MEMORANDUM

HUMAN FACTORS STUDY RESULTS AND LABEL AND LABELING REVIEW MEMO
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	December 5, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	(b) (4)
Product Name, Dosage Form, and Strength:	Zelsuvmi[a] (berdazimer) topical gel, 10.3%
Applicant/Sponsor Name:	LNHC, Inc.
TTT ID #:	2023-3362-1
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted their revised container label received on October 26, 2023 and November 27, 2023 for (b) (4) The Division of Dermatology and Dentistry (DDD) requested that we review the container label for (b) (4) (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous human factors study results review.[b]

2 CONCLUSION

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

[a] The proposed proprietary name for this NDA, Zelsuvmi, was found conditionally acceptable on June 20, 2023.
[b] Kumar, N. Human Factors Study Results Review for Zelsuvmi (NDA 217424). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 OCT 13. TTT ID No.: 2023-3362.

APPENDIX A. LABEL AND LABELING RECEIVED ON OCTOBER 26, 2023 AND NOVEMBER 27, 2023

Applicant's response to human factors study results label and labeling recommendations available from: \\CDSESUB1\EVSPROD\nda217424\0026\m1\us\111-info-amend\summary-of-changes-in-ifu-for-sn0026-26oct2023.pdf

Instructions for use (image now shown) available from: \\CDSESUB1\EVSPROD\nda217424\0030\m1\us\114-labeling\114a-draft-label\proposed-ifu-20231127-lnhc-clean.docx

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/s/

NEHA KUMAR
12/05/2023 03:27:51 PM

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12/05/2023 04:08:44 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	November 29, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217424
Product Name, Dosage Form, and Strength:	Zelsuvmi (berdazimer) topical gel, 10.3%
Applicant/Sponsor Name:	Novan, Inc.
TTT ID #:	2023-3359-1
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 21, 2023 for Zelsuvmi. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Zelsuvmi (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 label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and the Office of Pharmaceutical Quality (OPQ) is in alignment with revisions. We have no additional recommendations at this time.

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

[a] Fanari, M. Label and Labeling Review for Zelsuvmi (NDA 217424). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Aug 15. TTT ID No.: 2023-3359.

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/s/

MELINA N FANARI
11/29/2023 10:07:41 AM

MADHURI R PATEL
11/29/2023 03:46:29 PM

Clinical Inspection Summary

Date	10/23/2023
From	Stephanie Coquia, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Hamid Tabatabai, MD, Clinical Reviewer David Kettl, MD, Clinical Team Leader Strother Dixon, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
NDA #	217424
Applicant	LNHC, Inc.
Drug	Berdazimer (SB206 Gel)
NME (Yes/No)	Yes
Therapeutic Classification	Nitric oxide releasing agent and molluscum contagiosum (MC) virus gene expression inhibitor
Proposed Indication	For the topical treatment of MC in adult and pediatric patients (b) (4) of age and older
Consultation Request Date	2/10/2023
Summary Goal Date	11/5/2023
Action Goal Date	12/21/2023
PDUFA Date	1/5/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Novan Inc., submitted clinical data from Study NI-MC304 (NCT04535531) to support a New Drug Application (NDA 217424) for berdazimer for the topical treatment of molluscum contagiosum (MC) in adult and pediatric patients (b) (4) of age and older.

Three clinical investigators (Drs. Gibson, Jackson, and Forsha) and the Sponsor, Novan Inc., were inspected. The inspections did not find significant concerns regarding the study conduct, oversight, and management of the clinical trial or Good Clinical Practice (GCP) or regulatory compliance, and based on the results of these inspections, the data generated by the inspected clinical investigators and submitted by the applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

Novan Inc. seeks approval for an NDA for berdazimer indicated for the treatment of MC in adults and pediatric patients (b) (4) of age and older.

In support of this NDA, the Applicant submitted clinical data from a multi-center, randomized, double-blind, parallel-group, vehicle-controlled phase 3 trial in subjects with MC (Study NI-MC304). A treatment period of 12 weeks was followed by a safety follow-up period of 12 weeks.

The primary efficacy endpoint was the proportion of subjects achieving complete clearance of all treatable MC lesions at Week 12. Complete clearance was defined as the subject having zero (0) lesions (total number of lesions count: 0). The proportion of subjects achieving complete clearance of all treatable MC lesions at Week 8 was a secondary efficacy endpoint of interest. Lesion count was an investigator assessment. Berdazimer treatment arm results were compared to the vehicle treatment arm results.

Key eligibility criteria included:

- Subjects 6 months of age or older in good general health
- Between three and 70 treatable MC lesions at Baseline

Subjects were randomized 1:1 to Berdazimer or Vehicle Gel. Subjects or their caregivers applied the assigned gel to the affected areas once daily. Subjects or their caregivers were to apply the treatment on all lesions identified at Baseline and on any new lesions that arose during the treatment period for a minimum of 4 weeks and continue unless otherwise instructed by the investigator for up to 12 weeks.

A total of 55 clinical sites in the United States enrolled 984 subjects; 891 subjects were randomized (447 subjects to the Vehicle group and 444 subjects to the Berdazimer group). A total of 754 subjects completed the study (377 subjects in the Vehicle group and 377 subjects in the Berdazimer group). A total of 753 subjects completed 12 weeks of treatment (390 subjects in the Vehicle group and 363 subjects in the Berdazimer Group).

RESULTS

1. **Dr. Jane Gibson (Site 328)**
   675 7th Ave
   Bowling Green, KY 42101-6921

   Inspection Dates: June 5 – June 9, 2023

   This investigator was inspected as a routine PDUFA inspection for NI-MC304. This was the first FDA inspection of this investigator.

There were 27 subjects who signed the informed consent form (ICF); twenty-four subjects completed the study, and three subjects discontinued treatment due to adverse events (AEs).

The subject records for 15 of 24 subjects were reviewed, including records for 10 out of the 11 responders. Subject source records reviewed included: primary efficacy source records, diary logs, investigational product (IP) dispensing records, documentation of eligibility, local skin reaction (LSR) information, ICFs, paper case report forms (CRFs), emails, downloaded pictures, and paper worksheets. Data was recorded on paper CRFs that were provided by the Sponsor and then transferred to electronic CRFs (eCRFs) by the study coordinators.

Study-related records reviewed included: regulatory documents, institutional review board (IRB) approvals, monitoring records, temperature logs, training material, financial disclosures, and IP accountability records.

No discrepancies were identified between source records, the paper CRFs, eCRFs, and data listings reviewed. Specifically, for the primary efficacy endpoint, no discrepancies were identified between the source data and the data submitted to FDA. There were no unreported AEs; specifically, there were no discrepancies in the adverse event LSR source data, and there were no unreported scars. No unreported protocol deviations were identified.

2. Dr. Sarah C. Jackson (Site 332)
3525 Prytania St., Suite 321
New Orleans, LA 70115

Inspection Dates: June 12 – 15, 2023

This investigator was inspected as a routine PDUFA inspection for NI-MC304. This was the first FDA inspection of this investigator.

There were 28 subjects enrolled at the site. Eight subjects were lost to follow-up, one withdrew, and 19 subjects completed the study. All 28 subjects' records were reviewed for informed consent/assent, protocol compliance, and study eligibility. Source records were also reviewed for MC lesion counts, subject discontinuations, protocol deviations, AEs, and concomitant medications.

Study-related records reviewed included: IRB approvals, financial disclosure records, training certificates, monitoring records, sponsor correspondence, temperature logs, and IP accountability records.

There was no underreporting of AEs or significant protocol deviations identified. No discrepancies were identified between the source data and the sponsor line listings for the primary and secondary endpoints, specifically MC lesion counts in those recorded as having no lesions at Week 8 and Week 12. The same evaluator was used at Baseline and at the Week 12 visit (as per protocol) for all responders, except for Subject (b) (6) (assigned to Vehicle).

Reviewer comments: Although Subject (b) (6) *had a different evaluator at Baseline and Week 12, the protocol allows for a different evaluator "due to unforeseen circumstances." All evaluators at the site (two total) underwent training for MC lesion count assessment, and both Week 8 and Week 12 scores for Subject* (b) (6) *were the same (no lesions) with different evaluators. This single instance of a different MC lesion count evaluator is unlikely to change the overall study efficacy.*

3. Dr. Douglass W. Forsha (Site 345)
10654 S River Heights Dr Suite 210
South Jordan, UT 84095

Inspection Dates: August 21 – 24, 2023

This investigator was inspected as a routine PDUFA inspection for NI-MC304. The investigator previously was inspected on October 19 – 28, 2015, with the following observations noted: failure to follow the investigational plan, eCRFs not matching source data, and inadequate IP disposition record.

Twenty-five subjects were screened and randomized for the study; five subjects terminated the study early due to limited efficacy (two discontinuations and three lost to follow-up). The source documents for all subjects were reviewed. Subject source records reviewed included those related to eligibility, efficacy, LSRs, and informed consent.

Study-related records reviewed included: training records, signed investigator agreements, delegation of authority log, IRB correspondence, subject eligibility and enrollment log, financial disclosure forms, IP storage and accountability records, and monitoring records.

No underreporting of significant or serious protocol deviations was identified. No discrepancies were identified between the source documents and the data submitted to FDA related to safety or efficacy. Except for subjects (b) (6) the evaluator at Baseline was the same evaluator for Week 8 (secondary endpoint) and Week 12 (primary endpoint), as per the protocol.

Reviewer comment: All evaluators at the site underwent training for MC lesion count assessment, and the protocol allows for a different evaluator "due to unforeseen circumstances." Out of the above three subjects with a different evaluator between Baseline and Week 8 or Baseline and Week 12, only Subject (b) (6) *(treatment arm) was considered a responder. This single instance of a different MC lesion count evaluator is unlikely to change the overall study efficacy.*

4. Novan Inc. (Sponsor)
4020 Stirrup Creek Dr. Suite 110
Durham, NC 27703

Inspection Dates: June 5 – June 7, 2023

The Sponsor was inspected as a routine PDUFA inspection for NI-MC304. This was the first FDA inspection of this sponsor.

The inspection covered the following records: study organization and personnel, clinical trial registration, selection and monitoring of clinical investigators, selection of monitors, monitoring procedures/activities, quality assurance, AE reporting, data collection and handling, record retention, training, financial disclosure, electronic records and signatures, and IP accountability.

Monitoring document review (site visit logs, monitoring reports, signed investigator agreements, and financial disclosure documents) focused on the three clinical investigator sites chosen for inspection and five additional sites. No concerns were identified related to study monitoring, oversight, and data management.

{See appended electronic signature page}

Stephanie Coquia, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
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Jenn Sellers, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:
Review Division /Division Director/Shari Targum, MD
Review Division /Project Manager/Strother Dixon
Review Division/Cross Discipline Team Lead/David Kettl, MD
OSI/Office Director/Dave Burrow
OSI/ GCP Program Analysts/Yolanda Patague

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/s/

STEPHANIE F COQUIA
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MICHELE B FEDOWITZ
10/23/2023 03:20:04 PM

JENN W SELLERS
10/23/2023 03:23:36 PM

HUMAN FACTORS STUDY REPORT REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	October 13, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217424
Product Type:	Multiple ingredients product
Product Name, Dosage Form, and Strength:	Zelsuvmi[a] (berdazimer) topical gel, 10.3%
Device Constituent:	Gel with Dosing Guide
Rx or OTC:	Rx
Applicant/Sponsor Name:	LNHC, Inc.
Submission Date:	January 5, 2023; June 29, 2023; September 15, 2023
TTT ID #:	2023-3362
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

[a] The proposed proprietary name for this NDA, Zelsuvmi, was found conditionally acceptable on June 20, 2023. However, the Applicant used the name, (b) (4) throughout the human factors validation study.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results report submitted under NDA 217424 for Zelsuvmi (berdazimer).

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/ Appendix
Product Information/Prescribing Information	Section 1.1
Background Information Previous HF Reviews (DMEPA)	Section 1.2
Background Information on Human Factors Engineering (HFE) Process	Appendix A
Human Factors Validation Study Report	Appendix B
Information Requests Issued During the Review	Appendix C
Labels and Labeling	Appendix D
Detailed List of Use Errors, Use Difficulties, And Close Calls For Section 3.1	Appendix E

1.1 PRODUCT DESCRIPTION

Table 2. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Nitric oxide releasing agent
Active Ingredient (Drug or Biologic)	Berdazimer
Indication	Molluscum contagiosum (MC) in adult and pediatric patients (b) (4) of age and older
Route of Administration	Topical
Dosage Form	Topical gel
Strength	10.3%
Dose and Frequency	Dispense equal amounts from each tube per the Dosing Guide, mix together on the Dosing Guide and immediately apply an even thin layer once daily to each MC lesion for up to 12 weeks. Avoid application to uninvolved skin. Allow the gel to dry for 10 minutes after application and avoid transfer of the applied drug to other areas including the eye.
How Supplied	Each carton contains: • One tube of berdazimer sodium gel (blue label, 14 grams) • One tube of hydrogel (yellow label, 17 grams) • Dosing Guide • Instructions for use
Storage	• Prior to dispensing: Store in a refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze. • Dispensing instructions (b) (4) store at room temperature, between 68°F and 77°F (20°C to 25°C). Do not freeze. • Discard 60 days after removal from refrigeration.
Container Closure/Device Constituent	(b) (4)

	(b) (4)
Intended Users	Patients, caregivers
Intended Use Environment	Home

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

On May 31, 2023, we searched previous DMEPA reviews relevant to this current review using the terms, "IND 137015", "NDA 217424" and "berdazimer". Our search identified one previous review, and we considered our previous recommendations to see if they are applicable for this current review. See details below.

- On February 22, 2022, the Applicant submitted their HF validation study protocol under IND 137015 for berdazimer topical gel. We reviewed the protocol and provided

recommendations.[b] Aside from those listed in Section 2.2, the Applicant accepted our recommendations.

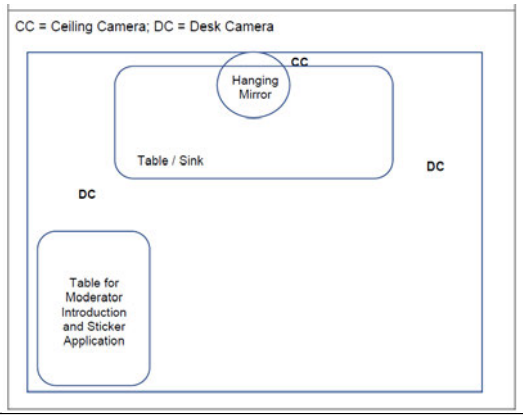
- On January 5, 2023, the Applicant submitted a new drug application (NDA) for Zelsuvmi (berdazimer) topical gel under NDA 217424. This submission included an HF validation study results report, which is the subject of this review.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details provided by the Applicant
Participants	• Group 1: 16 caregivers 18 years and older • Group 2: 15 adolescents ages 10 to 17 years
Training	No training or instruction provided to the participants
Test Environment and Materials	• To simulate MC lesions, small adesive stickers were applied to the 3- to 11-year-old children in group 1 and the 10 to 17-year-old participants in group 2. • Use of this product requires water and soap and waiting 10 minutes after application prior to putting on clothes, so the test environment was set up like a bathroom. There was water, soap, paper towels, and a mirror available. Test environment graphic: 

Sequence of Study	Simulated use Moderator interview for root cause analysis Knowledge assessment Moderator interview for root cause analysis

2.2 DISCUSSION OF STUDY METHODOLOGY

During the course of our review of the HF validation study, we noted that the Applicant did not implement all our HF validation study protocol recommendations.[b] We recommended to use mannequins instead of applying the gel to children and to incorporate use of a barrier that allows adolescent patient participants to use the placebo gel without having to apply it directly to the skin. However, the Applicant stated that the HF validation study protocol was approved by the Institutional Review Board (IRB). The Applicant did not use mannequins but instead had the participants apply the gel to stickers that were placed directly to the skin because that is "*reflective of a real-world scenario, in which a child may be moving around or talking to their guardian*". The Applicant did not incorporate a barrier because they conducted a screening, approved by IRB, to ensure participants were not allergic to the placebo ingredients. We find the Applicant's rationale to not use mannequins and barriers acceptable.

3 RESULTS AND ANALYSES

In this section, we have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), the Applicant's URRA, the participants' subjective feedback, the Applicant's RCA, and the Applicant's comments to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. We provide a discussion of the identified use tasks and knowledge task assessment, where we agree with the Applicant's conclusions and have no further recommendation or comment, in Appendix E.

In Table 4 below, we document our points of dissent with the Applicant's findings.

[b] Oguntimein, M. Human Factors Validation Study Protocol Review for berdazimer IND 137015. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 APR 12. TTT ID #.: 2022-402.

Table 4. Focused Analysis of Use Errors, Use Difficulties and Close Calls and DMEPA's Recommendations

Legend: **MC** = molluscum contagiosum; **UE** = use error; **CC** = close call; **UD** = use difficulty; **URRA** = use-related risk analysis; **RCA** = root cause analysis; **HFVS** = Human Factors Validation Study
Participants ID: AD = adolescent patient participant; **CG**: caregiver participant

Information Supplied by Applicant	DMEPA's Findings and Recommendations
Task: Squeeze Tube A (blue tube) gel on dosing lane to cover entire area of Tube A (blue tube) dosing lane and squeeze Tube B (yellow tube) gel on dosing lane to cover entire area of Tube B (yellow tube) dosing lane. Errors: UE (n = 1); Participant Type: AD = 1 Observed error(s): Participant only squeezed out enough gel to cover a quarter of each dosing lane. Relevant RCA/Subjective Feedback/Observation: Participant knew a full Dosing Guide would treat (b) (4) MC lesions remaining to cover with mixed gel and thought that they did not need the entire lanes' worth of product. Based on the Applicant's URRA, performing this task incorrectly or not at all may result in: MC lesions persisting.	
Applicant's Comments and Proposed Post-HFVS Mitigations: None	Our review of the instructions for use (IFU) indicates that the Step 3 statement, (b) (4) is confusing and may be misleading. We also note that the Agency has recommended the Applicant remove the phrase (b) (4) from the following sections in the Prescribing Information (PI): • Highlights Dosage and Administration statement, "*Mix together and immediately apply a thin layer of Zelsuvmi* (b) (4) (b) (4) • Section 2 statement, "*Immediately apply Zelsuvmi* (b) (4) *as even thin layer* (b) (4). Additionally, the IFU Step 2 statements, "*Squeeze gel onto blue lane to cover entire area of the lane*" and "*Squeeze gel onto yellow lane to cover* (b) (4) *entire area of the lane*" lack prominence. Based on the subjective feedback (participant stated that since they had (b) (4) remaining to cover with mixed gel, they only used a quarter of the dosing lanes), the Agency's PI recommendation, and our overall assessment, we find that the IFU step 3, (b) (4) should be removed. Additionally, Step 2 can be improved to emphasize covering the entire areas

<table>
<tr><td></td><td>of the Dosing Guide lanes. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.</td></tr>
<tr><td>Task: Put IFU back in carton
<table><tr><td>Errors:</td><td>Participant Type:</td></tr><tr><td>UE (n = 13)</td><td>CG = 3; AD = 10</td></tr><tr><td>CC (n = 2)</td><td>CG = 2</td></tr></table>Observed error(s): Participants did not put IFU back into carton after completing the prior tasks.
Relevant RCA/Subjective Feedback/Observation:
Participants stated that they would store the IFU separately, such as in a Ziplock bag, since that is where they keep all their instructions.
Participant said they would memorize the instructions, so they could throw out the IFU.
Participant stated that in the latter portion of the IFU, the IFU states to put the Dosing Guide and tubes, but not the IFU, in the carton.
Participants stated that they would put the IFU back in the carton at home but did not feel the need to do so in the study setting.
Based on the Applicant's URRA, performing this task incorrectly or not at all may result in MC lesions persisting.</td><td></td></tr>
<tr><td>Applicant's Comments and Proposed Post-HFVS Mitigations: None</td><td>Our review of the IFU indicates that Step 6 instructs users to put the Dosing Guide and tubes, but not the IFU, in the carton. Based on the subjective feedback (a participant that stated the latter part of the IFU states to put the Dosing Guide and tubes, but not the IFU, in the carton) and our overall assessment, we find that Step 6 can be improved to include instructions to put the IFU back in the carton. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.</td></tr>
<tr><td>Task: Wash hands after storage
<table><tr><td>Errors:</td><td>Participant Type:</td></tr><tr><td>Incorrect (n = 10)</td><td>CG = 6; AD = 4</td></tr></table>Observed error(s): Participants did not wash their hands after storing away the product.
Relevant RCA/Subjective Feedback/Observation:
Participants stated that the hand washing step in the IFU was not salient, since they did not notice the information.</td><td></td></tr>
</table>

• Participants stated they usually do not wash their hands after product use at home. • Participants stated that while they were washing the Dosing Guide, their hands were also being washed. **Based on the Applicant's URRA, performing this task incorrectly or not at all may result in** mild eye irritation.	
Applicant's Comments and Proposed Post-HFVS Mitigations: none	Our review of the IFU indicates that Step (b) (4) . However, this statement is under the header "*Step* (b) (4) and grouped together with instructions (b) (4) Additionally, although the header states, "*Step* (b) (4) These inconsistencies may cause confusion. (b) (4) Based on the subjective feedback (some participants stated that the hand washing step in the IFU was not salient, since they did not notice the information) and our overall assessment, we find that the instruction to support this task is not prominent. **We provide our recommendation in Table A to address this concern.** We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.
Knowledge task: How do you mix the gels? Would you ever mix gels anywhere else besides the Dosing Guide? **Errors:** Incorrect (n = 8); **Participant Type:** CG = 4; AD = 4 **Observed error(s):** Participants indicated that they would mix the gels on other items, such as a bowl, plate, directly on skin. **Relevant RCA/Subjective Feedback/Observation:** • Participants focused on ensuring they had equal parts of both gels and stated that as long as they had equal amounts of the gels, they could use items other than the Dosing Guide to measure and mix the gels. • Participant stated that the IFU information on only mixing on the Dosing Guide and not mixing on skin was not salient in the IFU, since they did not notice the information.	

<table>
<tr><td>Based on the Applicant's URRA, performing this task incorrectly or not at all may result in MC lesions persisting.</td><td></td></tr>
<tr><td>Applicant Comment and Proposed Mitigations: None</td><td>Our review of the IFU indicates that it contains instructions to only use the Dosing Guide to mix the gels. However, the IFU does not include the reason why it is important for users to only use the Dosing Guide when mixing the gels. Additionally, based on the subjective feedback (participant stated that the IFU information on only mixing on the Dosing guide and not mixing on skin was not salient, since they did not notice the information), and our overall assessment, we find that the instruction to support this task is not prominent. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.</td></tr>
<tr><td>Knowledge task: Once the medication is applied, how long do you need to wait before getting your skin wet?
<table><tr><td>Errors:</td><td>Participant Type:</td></tr><tr><td>Incorrect (n=7)</td><td>CG = 3; AD = 4</td></tr></table>Observed error(s): Participants did not know the amount of time needed to wait before showering or swimming after treating the MC lesions.</td><td></td></tr>
<tr><td>Relevant RCA/Subjective Feedback/Observation:
Participants stated that the information was not salient in the IFU, since they did not notice the information.
Participants did not realize they could refer to the IFU during the knowledge task questions and did not remember relevant information.
Participant did not turn the IFU to the back, where the relevant information is located.</td><td>The Applicant's RCA is incomplete because the Applicant did not investigate why one participant did not turn the IFU to the back.</td></tr>
<tr><td>Based on the Applicant's URRA, performing this task incorrectly or not at all may result in MC lesions persisting.</td><td></td></tr>
<tr><td>Applicant Comment and Proposed Mitigations: None</td><td>Although the Applicant's RCA related to the participant who did not turn the IFU to the back is incomplete, our review of the IFU indicates the front of the IFU contains the statement, "Turn to the back (b) (4) more instructions". Additionally, we note that because the IFU is in a two-column format, our colleagues in the Division of Medical Policy Programs (DMPP) recommend the Applicant move the IFU statement to underneath the second column so that patients do not turn to the instructions on the back of the page after reading the first column.

Our review of the IFU indicates that it contains instructions (b) (4) However, based on the subjective feedback (participants stated that the information was not</td></tr>
</table>

	salient in the IFU, since they did not notice the information), and our overall assessment, we find that the instruction to support this task is not prominent. **We provide our recommendation in Table A to address this concern.** We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.
Knowledge task: Once the medication is applied, how long do you need to wait to put clothes on treated skin? **Errors:** Incorrect (n=7); **Participant Type:** CG = 3; AD = 4 **Observed error(s):** Participants did not know the amount of time needed to wait before putting clothes over treated skin.	[redacted]
Relevant RCA/Subjective Feedback/Observation: • Participant remembered seeing the relevant information initially in the IFU but did not specifically remember what the IFU listed and stated that since their child already had clothes on, they did not pay attention to the relevant instructions. • Participants stated that the information was not salient in the IFU, since they did not notice the information. • Participant chose not to refer to the IFU throughout the study and another participant did not turn the IFU to the back, where the relevant information is located.	The Applicant's RCA is incomplete because the Applicant did not investigate why one participant did not refer to the IFU throughout the study and why the other participant did not turn the IFU to the back.
Based on the Applicant's URRA, performing this task incorrectly or not at all may result in MC lesions persisting.	[redacted]
Applicant Comment and Proposed Mitigations: None	Although the Applicant's RCA related to the participant who did not refer to the IFU at all and the participant who did not turn the IFU to the back were incomplete, our review of the IFU indicates that the IFU is folded in the carton with the heading, "*Instructions for Use*" facing the user. See image below: 

	Additionally, our review of the IFU indicates the front of the IFU contains the statement, "*Turn to the back* (b) (4) *more instructions*". Because the IFU is in a two-column format, our colleagues in DMPP recommend the Applicant move the IFU statement to underneath the second column so that patients do not turn to the instructions on the back of the page after reading the first column. Our review of the IFU indicates that it contains instructions to wait at least 10 minutes after applying the gel before putting clothes on the skin. However, based on the subjective feedback (participants did not notice these instructions), and our overall assessment, we find that the instruction to support this task is not prominent. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.

3.1 ANALYSIS OF THE REMAINING IDENTIFIED ISSUES

The HF validation study reported showed issues with the tasks evaluated by simulated use and knowledge-based assessments (KBAs) listed in Appendix E. However, based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), the Applicant's root cause analysis, our evaluation of the residual risks, we find the proposed user interface has been appropriately designed. The labels and labeling include information that is prominently, and we did not identify recommendations to address the identified issues with the tasks in Appendix E.

3.2 LABELS AND LABELING

Table A below includes the identified medication error issues with the submitted instructions for use (IFU) and berdazimer and hydrogel tube caps based on the HF study results, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. Additionally, we note that the DMEPA 1 naming and labeling review team evaluated product specific label and labeling under separate cover.[3]

[3] Fanari, M. Label and labeling review for berdazimer NDA 217424. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 15. TTT ID #.: 2023-3359.

Table A: Identified Issues and Recommendations for LNHC, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The Step 4 statement, (b) (4) is confusing and may be misleading. This statement is also inconsistent with the Prescribing Information (PI).	Per the use-related risk analysis (URRA), if the user does not cover the entire dosing lanes there is risk of molluscum contagiosum (MC) lesions persisting. The human factors (HF) validation study results identified subjective feedback that indicated that the participant who had (b) (4) remaining MC lesions to cover with the mixed gel thought that they only needed to cover a quarter of the dosing lanes (b) (4) Additionally, we expect the information in the IFU to align with the information in the Prescribing Information (PI). Specifically, we recommended you remove the phrase (b) (4) in the following PI statements: • Highlights Dosage and Administration section, "*Mix together and*	Remove the Step 4 statement, (b) (4)

		immediately apply a thin layer of Zelsuvmi [redacted] • Section 2 Dosage and Administration, "*Immediately apply Zelsuvmi* [redacted] *as even thin layer* [redacted] We expect the IFU information is aligned with the PI information. As such the same edits should be made in the IFU.	
2.	The task to cover the entire Dosing Guide lanes in the section Step 2 statements, "*Squeeze gel onto blue lane to cover entire area of the lane*" and "*Squeeze gel onto yellow lane to cover the entire area of the lane*" lacks prominence.	Per the URRA, if the user does not cover the entire dosing lanes there is risk of MC lesions persisting. The HF validation study results identified subjective feedback that indicated that the participant who had [redacted] remaining MC lesions to cover with the mixed gel thought that they only needed to cover a quarter of the dosing lanes.	Increase the prominence of the task to cover the entire lanes in the Step 2 statements, "*Squeeze gel onto blue lane to cover entire area of the lane*" and "*Squeeze gel onto yellow lane to cover the entire area of the lane*".
3.	Step 6 does not include instructions to put the IFU back in the carton after use. Specifically, Step 6 states, "*Put Dosing Guide back in box. Secure caps on tubes and*	Per the URRA, if this task is omitted or performed incorrectly then there is risk of MC lesions persisting. The HF validation study identified subjective feedback that indicated	Revise Step 6 to include instructions to put the IFU back in the carton.

	place back in box" but does not state to put the IFU back in the carton.	that the participant saw that the latter portion of the aforementioned IFU Step 6 statements instructs to put Dosing Guide and tubes, but not the IFU, in the carton.	
4.	The location of the Step (b) (4) statement, (b) (4) , is confusing because the statement is under the header, "*Step* (b) (4) and grouped together with instructions (b) (4) This decreases prominence of the task, (b) (4) Additionally, we note an inconsistency between the Ste (b) (4) Specifically, the header states, "*Step* (b) (4) (b) (4)	Per the URRA, if this task is omitted or performed incorrectly there is risk of mild eye irritation. The HF validation study identified subjective feedback that indicated that the participants thought the (b) (4) step in the IFU was not salient, since they did not notice the information. Additionally, we are concerned that the aforementioned inconsistency between the Step (b) (4) header and the (b) (4) in the step may cause confusion.	Move the instructions, (b) (4) away from Step (b) (4) For example, create a separate step for this (b) (4) task and place the (b) (4) with that separate step.

5.	The *Important Information You Need to Know Before Applying Zelsuvmi* section statements, "*The gels in Tube A and Tube B must be mixed together on the Dosing Guide before applying to your skin*" and "*Only mix gels on Dosing Guide. Do not mix gels directly on skin or in palm of hand*" lack prominence.	Per the URRA, if this task is omitted or performed incorrectly there is risk of MC lesions persisting. The HF validation study identified subjective feedback that indicated that the participants thought that the IFU information regarding only mixing on the Dosing Guide was not salient since they did not notice the information.	Increase the prominence of the *Important Information You Need to Know Before Applying Zelsuvmi* section statements, "*The gels in Tube A and Tube B must be mixed together on the Dosing Guide before applying to your skin*" and "*Only mix gels on Dosing Guide. Do not mix gels directly on skin or in palm of hand*".
6.	The IFU does not include the reason why it is important for users to only use the Dosing Guide when measuring and mixing the gels. Specifically, the *Important Information You Need to Know Before Applying Zelsuvmi* section states, "*The gels in Tube A and Tube B must be mixed together on the Dosing Guide before applying to your skin*" and "*Only mix gels on Dosing Guide. Do not mix gels directly on skin or in palm of hand*", but not the reasoning for these instructions.	Per the URRA, if this task is omitted or performed incorrectly there is risk of MC lesions persisting. The HF validation study identified subjective feedback that indicated that since the IFU does not include the reason why it is important for users to only use the Dosing Guide when measuring and mixing the gels, participants thought that if they had equal amounts of the gels, they could use items other than the Dosing Guide, such as their skin or a plate, to measure and mix the gels.	Include the reason why it is important for users to only use the Dosing Guide when measuring and mixing the gels.

7.	The post-Step 4 statements, (b) (4) and "*Wait at least 10 minutes after applying gel before putting on clothes*" lack prominence.	Per the URRA, if this task is omitted or performed incorrectly there is risk of persisting MC lesions. The HF validation study identified subjective feedback that participants did not notice this information since it was not salient.	Increase the prominence of the post-Step 4 statements, "(b) (4) and "*Wait at least 10 minutes after applying gel before putting on clothes*".
8.	The *Important Information You Need to Know Before Applying Zelsuvmi* section statement states, "*Make sure to put the* (b) (4) *cap back onto the* (b) (4) *tube*". However, the IFU does not state what users should do if they mix the gel tube caps.	Per the URRA, if the user mixes the cap for the gel tubes this could lead to lack of drug efficacy and there is risk of MC lesions persisting. As such, in order to prevent lack of drug efficacy and persisting MC lesions, the IFU should include what users should do if they mix the gel tube caps.	Include information on what users should do if they mix the gel tube caps.
Berdazimer and hydrogel tube caps			
9.	The *Important Information You Need to Know Before Applying Zelsuvmi* section statement states, "*Make sure to put the* (b) (4) *cap back onto the* (b) (4) *tube*". (b) (4)	Per the URRA, if the user mixes the cap for the gel tubes this could lead to lack of drug efficacy and there is risk of MC lesions persisting. (b) (4)	Include differentiating characteristic(s) between berdazimer and hydrogel tube caps. (b) (4)

	(b) (4)		

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, and use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division of Dermatology and Dentistry (DDD) convey Table A in its entirety to the Applicant. These changes can be implemented without submitting additional HF validation testing data for Agency review.

4.1 RECOMMENDATIONS FOR LNHC, INC.

Our evaluation of your human factors (HF) validation study indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A, and we recommend that you implement these recommendations and submit the revised label and labeling for our review prior to the approval of this new drug application. We have determined that in this instance, you may implement these revisions without submitting additional human factors validation testing data for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

\\CDSESUB1\EVSPROD\nda217424\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscumcontagiosum\5354-other-stud-rep\ni-hf104\hfe-summary-report-v1-0.pdf .

APPENDIX B. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\EVSPROD\nda218026\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\aci\5354-other-stud-rep\api-hct-s1\5-3-5-4-pd-rpt-0612-human-factors-study-report.pdf
The use-related risk analysis can be accessible in EDR via:
\\CDSESUB1\EVSPROD\nda217424\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscumcontagiosum\5354-other-stud-rep\ni-hf104\use-related-risk-analysis-v4-0.pdf
The root cause analysis can be accessible in EDR via:
\\CDSESUB1\EVSPROD\nda217424\0017\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscumcontagiosum\5354-other-stud-rep\ni-hf104\appendix-8-root-cause-analysis.pdf

APPENDIX C. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On June 27, 2023, we issued an information request (IR) asking the Applicant to provide their root cause analysis by task order, rather than participant order, and to provide participant demographics.
On June 29, 2023, the Applicant provided an acceptable response that can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda217424\0017\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscumcontagiosum\5354-other-stud-rep\ni-hf104\appendix-8-root-cause-analysis.pdf

On September 13, 2023, we issued an IR asking the Applicant for the specific questions asked during the knowledge task assessment.
On September 15, 2023, the Applicant provided an acceptable response that can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda217424\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscumcontagiosum\5354-other-stud-rep\ni-hf104\nov003ntg01 (b) (4) v3-01sep2022.pdf and \\CDSESUB1\EVSPROD\nda217424\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscumcontagiosum\5354-other-stud-rep\ni-hf104\nov003ntg02- (b) (4) -v3-1-06sep2022.pdf

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following Zelsuvmi labels and labeling submitted by LNHC, Inc.

- Container labels received on January 5, 2023
- Carton labeling received on January 5, 2023
- Dosing Guide received on January 10, 2023
- Instructions for use (image not shown) received on March 22, 2023, available from \\CDSESUB1\EVSPROD\nda217424\0009\m1\us\114-labeling\114a-draft-label\sb206-ppi-and-ifu-word.docx
- Prescribing Information (image not shown) received on March 20, 2023, available from \\CDSESUB1\EVSPROD\nda217424\0008\m1\us\114-labeling\114a-draft-label\sb206-uspi-labeling-word-20230317-redline.docx

D.2 Label and Labeling Images

Container labels

(b) (4)

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

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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:	August 28, 2023
To:	Strother Dixon, PharmD Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** David Foss, PharmD, MPH, BCPS, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ZELSUVMI (berdazimer)
Dosage Form and Route:	topical gel
Application Type/Number:	NDA 217424
Applicant:	Novan, Inc.

1 INTRODUCTION

On January 5, 2023, Novan, Inc. submitted for the Agency's review an original New Drug Application (NDA) 217424 for ZELSUVMI (berdazimer) topical gel, with a proposed indication for the treatment of molluscum contagiosum (MC) in adults and pediatric patients (b) (4) of age and older.

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 Dermatology and Dentistry (DDD) on February 2, 2023 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ZELSUVMI (berdazimer) topical gel.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft ZELSUVMI (berdazimer) topical gel PPI and IFU received on March 22, 2023, and received by DMPP and OPDP on August 14, 2023.
- Draft ZELSUVMI (berdazimer) topical gel Prescribing Information (PI) received on March 20, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 14, 2023.
- Approved YCANTH (cantharidin) topical solution labeling dated July 21, 2023.

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 and IFU 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.

In our collaborative review of the PPI and IFU we:

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

- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are 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 and IFU 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 and IFU.

Please let us know if you have any questions.

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08/28/2023 04:39:31 PM

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

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

Memorandum

Date: August 16, 2023

To: Strother Dixon, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Hamid Tabatabai, Clinical Reviewer, DDD

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZELSUVMI™ (berdazimer) topical gel

NDA: 217424

Background:

In response to DDD's consult request dated February 2, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Zelsuvmi.

PI/PPI/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 14, 2023, and our comments are provided below.

OPDP comments on the proposed PPI/IFU will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on August 14, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 15, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 217424
Product Name, Dosage Form, and Strength:	Zelsuvmi (berdazimer) topical gel, 10.3%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novan, Inc.
FDA Received Date:	January 5, 2023, January 10, 2023, March 20, 2023, March 22, 2023
TTT ID #:	2023-3359
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 REASON FOR REVIEW

As part of the approval process for Zelsuvmi (berdazimer) topical gel, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Zelsuvmi prescribing information (PI), patient information (PPI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C– N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 DISCUSSION AND RECOMMENDATIONS

The proposed container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. Specifically, the identification of each tube should be revised as Tube A ([(b) (4)] and Tube B [(b) (4)] to ensure patients utilize both tubes for product preparation and administration. We collaborated with the Office of Pharmaceutical Quality (OPQ) and provide proposed recommendations to minimize the risk for medication error in Section 4 for Novan, Inc. (note these recommendations have already been sent to Novan). In addition, we collaborated with DDD to provide comments to the PI. DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR NOVAN, INC. (Note these comments have already been provided to Novan)

Container Labels, Carton Labeling and Kit Label (All)

1. In accordance with 21 CFR 201.55, the [redacted] (b) (4) statement should be deleted and replaced with the statement of dosage "[Recommended] Dosage: see Prescribing Information".

2. Revise the storage temperature statement to include units of measurement following the first numbers of the temperature range (e.g. 20°C -25°C).

3. The [redacted] (b) (4) statement should be revised (see below) and relocated to the last sentence of the storage section:

   'Discard 60 days after removal from refrigeration.'

4. We recommend revising the 'Dispensed date' statement as follows:

   Discard after ___/____/____

   In addition, this statement is only needed on the kit carton labeling and should be removed from all other labels and labeling.

5. The drug product established name of (berdazimer) gel should be displayed as follows:

   (berdazimer) topical gel

6. The individual tubes should be renamed as Tube A [redacted] (b) (4) and Tube B [redacted] (b) (4) and revised as detailed below.

Carton Labeling (Kit)

1. We reference our June 30, 2023 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Zelsuvmi, was found conditionally acceptable. We recommend replacing [redacted] (b) (4) **" with the conditionally acceptable proprietary name, Zelsuvmi, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.

2. We recommend revising the display of the kit contents as follows:

   Contents:
   Tube A (14 g): Containing 240 mg of berdazimer sodium
   Tube B (17 g): Containing hydrogel

1 Dosing Guide
Prescribing Information
Patient Information
Instruction for Use

3. Side panel
   Tube A contains: Berdazimer sodium 240 mg and cyclomethicone, hexylene glycol, hydroxypropyl cellulose, and isopropyl alcohol

   Tube B contains: benzoic acid, carboxymethylcellulose sodium, cyclomethicone, ethanol, glycerin, potassium phosphate monobasic, and purified water

4. Back panel:
   After mixing, each gram of ZELSUVMI contains berdazimer 103 mg (equivalent to 109 mg berdazimer sodium)

Carton Labeling (Tube A and B)

Primary Display Panel of Tube A

Tube A (1 of 2)
REQUIRES MIXING: For use ONLY in combination with Tube B, in accordance with the Instructions for Use.
For topical use ONLY, NOT for ophthalmic, oral or intervaginal use.
Contains berdazimer sodium 240 mg
NET WT. 14 g

Side panel of Tube A

- Revise directions to read "Directions: Apply as directed in the Instructions For Use for ZELSUVMI (berdazimer) topical gel"
- Include the following tube content statement:
  - [redacted] (b) (4) berdazimer sodium and cyclomethicone, hexylene glycol, hydroxypropyl cellulose, and isopropyl alcohol

Primary Display Panel of Tube B

Tube B (2 of 2)
REQUIRES MIXING: For use ONLY in combination with Tube A, in accordance with the Instructions for Use.
For topical use ONLY, NOT for ophthalmic, oral or intervaginal use.
NET WT. 17 g

Side panel of Tube B

- Revise directions to read "Directions: Apply as directed in the Instructions For Use for ZELSUVMI (berdazimer) topical gel"

- Include the following tube content statement:
    - Contains benzoic acid, carboxymethylcellulose sodium, cyclomethicone, ethanol, glycerin, potassium phosphate monobasic, and purified water

Container Labels (Tube A and B)

Tube A (1 of 2)

REQUIRES MIXING: For use ONLY in combination with Tube B, in accordance with the Instructions for Use.
For topical use ONLY, NOT for ophthalmic, oral or intervaginal use.
Contains berdazimer sodium 240 mg
NET WT. 14 g

Tube B (2 of 2)
REQUIRES MIXING: For use ONLY in combination with Tube A, in accordance with the Instructions for Use.
For topical use ONLY, NOT for ophthalmic, oral or intervaginal use.
NET WT. 17 g

Dosing Card

The [redacted] (b) (4) strip should be renamed as Tube A and the [redacted] (b) (4) strip should be renamed as Tube B.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zelsuvmi that Novan, Inc. submitted on March 8, 2023.

Table 2. Relevant Product Information for Zelsuvmi	
Initial Approval Date	N/A
Active Ingredient	berdazimer sodium
Indication	topical treatment of molluscum contagiosum (MC) in adult and pediatric patients (b) (4) of age and older.
Route of Administration	topical
Dosage Form	topical gel
Strength	10.3%
Dose and Frequency	Dispense equal amounts from each tube per the dosing guide, mix together on the dosing guide and immediately apply an even thin layer once daily to each molluscum lesion for up to 12 weeks. Avoid application to uninvolved skin. Allow the gel to dry for 10 minutes after application and avoid transfer of the applied drug to other areas including the eye.
How Supplied	carton box containing: • One tube of Berdazimer sodium gel (blue label, 14 gram) • One tube of Hydrogel (yellow label, 17 gram) • Dosing Guide • Instructions For Use
Storage	Prior to Dispensing: Store in a refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze. Dispensing Instructions (b) (4) store at room temperature, between 68°F and 77°F (20°C to 25°C). Do not freeze.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 21, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, 'berdazimer'. Our search identified one previous reviews[a] , and we considered our previous recommendations to see if they are applicable for this current review.

[a] Oguntimein, M. Human Factors Protocol Review for berdazimer (IND 137015). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 APR 12. OSE RCM No.: 2022-107.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Zelsuvmi labels and labeling submitted by Novan, Inc.

- Container labels received on January 5, 2023
- Carton labeling received on January 5, 2023
- Dosing Card Labeling received on January 10, 2023
- Patient Information, Instructions for Use received on March 22, 2023, available from \\CDSESUB1\EVSPROD\nda217424\0009\m1\us\114-labeling\114a-draft-label\sb206-ppi-and-ifu-word.docx
- Prescribing Information (Image not shown) received on March 20, 2023, available from \\CDSESUB1\EVSPROD\nda217424\0008\m1\us\114-labeling\114a-draft-label\sb206-uspi-labeling-word-20230317-redline.docx

F.2 Label and Labeling Images

Container label(s)

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

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

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