CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217424Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	217424
Applicant Name	Novan, Inc.
Drug Product Name	ZELSUZMI (berdazimer) topical gel
Dosage Form	Gel
Proposed Strength(s)	10.3% (equivalent to 10.9% berdazimer sodium)
NDA Classification	Type 1 - NME
Route of Administration	Topical
Maximum Daily Dose	2 g
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of molluscum contagiosum in adults and pediatric patients (b) (4) of age and older
Drug Product Description	The drug product consists of two gels; a (b) (4)% w/w berdazimer sodium in a white to off-white opaque (b) (4) isopropyl alcohol gel, and a proton donating hydrogel as a white to off-white translucent to opaque gel. The two gel components are stored in separate, identical aluminum tubes with a white reverse-taper puncture tip (RTPT) (b) (4) cap. At the point of use, equal volumes (0.5 mL each) are mixed and then applied to the skin lesions. **The mixed gel results in the labeled strength of 10.3% berdazimer.** The Applicant developed and validated an IVRT method that monitors the release rate of NO from SB206 gel. This method involves direct monitoring of berdazimer sodium decomposition in the admixture.

Co-packaged product information	The two gel components are packaged in separate, identical aluminum tubes to preserve stability of the active gel and prevent unintended loss of nitric oxide.		
Device information	N/A		
Storage Temperature/ Conditions	Prior to dispensing, 2°C – 8°C (36°F – 46°F). When dispensed from the pharmacy, patients should store the drug product at room temperature 20°C – 25°C (68°F – 77°F). The product should be disposed of 60 days after dispensing and storage at room temperature. Product contains alcohol and should be kept away from open flame.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Friedrich Burnett	Lawrence Perez
	Drug Product/ Labeling	Jane Chang (R1) Caroline Strasinger (R2/Labeling)	Caroline Strasinger (R1) Nina Ni (R2) Julia Pinto (Labeling)
	Manufacturing	Laurimer Kulian-Torres	Cassie Abellard
	Biopharmaceutics	Kalpana Paudel	Tapash Ghosh
	Microbiology	Marijke Koppenol-Raab	David Anderson
	Environmental	Xiaoqin Wu	James Laurenson
	RBPM	Rajani Ranga	
	ATL	Caroline Strasinger	
Consults	PQLC		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: A shelf-life of 28 months is supported for the drug product when stored refrigerated at 2ºC - 8ºC (36ºF - 46ºF). Do not freeze. When dispensed from the pharmacy, patients should store the drug

product at room temperature 20ºC - 25ºC (68ºF - 77ºF). The product should be disposed of 60 days after being stored at room temperature.

b. Additional Comments for Action – Not Applicable

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends **APPROVAL** of NDA 217424 for commercialization of ZELSUZMI (berdazimer) topical gel, 10.3%. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall Manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

On 15-DEC-2023 the applicant provided updated labels and labeling which included the %v/v ethanol (13%) in the PI and on the Kit and Tube B cartons. On 15-DEC-2023 the applicant included a statement regarding flammability (Product contains alcohol and should be kept away from open flame) in the PI and on all cartons.

Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Review & EI Statement - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments: N/A

Application Technical Lead Name and Date:
Caroline Strasinger, PhD
18-DEC-2023

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(b) (4)

R REGIONAL INFORMATION

Environmental

US Market projection for berdazimer topical gel from 2024 to 2028 was provided (see Section 1.12.14). Expected Introduction Concentration (EIC) of (b) (4) ppb was calculated based on the market projections of approximately (b) (4) kilograms thru 2028.

EIC-Aquatic (ppb) 1 = A × B × C × D where:

A = (b) (4) kg/year produced for direct use (as drug substance)
B = 1/liters per day entering publicly owned treatment works (i.e., 1.071 x 10^{11} liter per day)
C = year/365 days
D = 10^9 mcg/kg (conversion factor)

EIC-Aquatic (ppb) = ((b) (4)) × [1/(1.071 × 10^{11})] × (1/365) × (10^9) = (b) (4) ppb

Assessor's Comment: ***Adequate***

The EA team has reviewed the claim of categorical exclusion and they found that the production of the API should be (b) (4) kg/yr rather than what the applicant used for EIC calculation ((b) (4) kg). The following comments were provided in an email dated 3/30/2023 from Environmental Assessor, Xiaoqin Wu.

> "The applicant submitted a claim of categorical exclusion (CE) from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. They also provided the required statement of no extraordinary circumstances in accordance with 21 CFR 25.15. The active ingredient berdazimer sodium is expected to have a max annual production of (b) (4) kg/yr and an EIC of (b) (4) ppb. Neither berdazimer nor its hydrolyzed product seem to have hormonal

activity. Therefore, FDA concluded that approval of this application would have no significant environmental impact. The claim of CE is acceptable."

Methods Validation or Verification Package

N/A

Comparability Protocols

N/A

Post-Approval Commitments

N/A

Lifecycle Management Considerations

N/A

Primary Drug Product Assessor Name and Date:

Caroline Strasinger, Ph.D.
Master Chemistry Reviewer
OPQ/ONDP/DNDP II/Branch 4
11/02/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Nina Ni, Ph.D.
Branch Chief
OPQ/ONDP/DNDP II/Branch 4
11/13/2023

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 11/21/2023 11:03:09AM
GUID: 5051dfdd000013b995075b4d54108ed8

Nina Ni

Digitally signed by Nina Ni
Date: 11/13/2023 03:13:54PM
GUID: 502d1ab500002afbbe642f8f37136920

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CHAPTER IV: LABELING

General Statements:
PQLC was consulted to discuss and confirm the strength presentation and all aspects of label and labeling. DMEPA, OPQ, and PQLC collectively decided that identifying the two tubes as Tube A and Tube B was the clearest and least confusing approach. Tube A contains a berdazimer (b) (4) gel and Tube B contains a hydrogel. This collective approach is reflected throughout the review below.

On December 6, 2023, the OPPQ-PQL team further requested that the %v/v alcohol (i.e., ethanol) in Tube B be included in the PI and on the appropriate cartons and to request the applicant to include a flammability statement if applicable. See the Appendix 1 for summary of communication from PQL.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	Include "topical gel" 13-NOV-2023 – This was agreed to by the applicant
Route(s) of administration	Adequate	Topical
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Edit for clarity and incorporate Tube A and Tube B.

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

		13-NOV-2023 – This was agreed to by the applicant
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	The drug product contains a salt. The information should be modified to state the strength is 10.3% berdazimer. 13-NOV-2023 – This was agreed to by the applicant

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Description of tubes should be revised to Tube A and Tube B for clarity. Additional areas revised for clarity by other disciplines; no issues with proposed revisions from OPQ 13-NOV-2023 – This was agreed to by the applicant

Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Revised for clarity by other disciplines; no issues with proposed revisions from OPQ
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Change to Topical Gel: 13-NOV-2023 – This was agreed to by the applicant
Strength(s) in metric system	Adequate	Revisions requested to be consistent with salt policy. 13-NOV-2023 – This was agreed to by the applicant
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	Revisions requested to be consistent with salt policy. To avoid confusion the equivalency statement appears only in section 11 of the PI. 13-NOV-2023 – This was agreed to by the applicant
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Revisions requested for clarity 13-NOV-2023 – This was agreed to by the applicant
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

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

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	Proprietary and established name changes requested 13-NOV-2023 – This was agreed to by the applicant
Dosage form(s) and route(s) of administration	Adequate	Dosage form should include route (topical) 13-NOV-2023 – This was agreed to by the applicant
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	Revise for clarity and alignment with Salt Guidance 27-NOV-2023 – This was agreed to by the applicant
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	List in alphabetical order 13-NOV-2023 – This was agreed to by the applicant
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Inadequate	Tube B contains ethanol. Applicant was requested to include %(v/v) ethanol in section 11 inactive ingredient list 12-DEC-2023 – This was communicated to the applicant
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	Nitric oxide releasing agent (confirmed by Nonclinical) 27-NOV-2023 – This was agreed to by the applicant
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Adequate	Revise for clarity 27-NOV-2023 – This was agreed to by the applicant

Section 11 (DESCRIPTION) Continued

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Revise to topical gel 13-NOV-2023 – This was agreed to by the applicant
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Revise for clarity 13-NOV-2023 – This was agreed to by the applicant
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Revise for clarity. Change to a discard after date. 13-NOV-2023 – This was agreed to by the applicant 12-DEC-2023 - Applicant was requested to add a statement regarding flammability of formulation or provide evidence the product is not flammable.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Revise for clarity 13-NOV-2023 – This was agreed to by the applicant
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Not provided 27-NOV-2023 – Updated by the applicant to read Manufactured for: EPIH SPV, LLC Wilmington, Delaware 19801

3.0 CONTAINER AND CARTON LABELING

The labels provided below are the original submission labels.

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	Revise to (berdazimer) topical gel 14-NOV-2023 – Agreed to by the applicant
Strength(s) in metric system	Adequate	Revise as recommended below 14-NOV-2023 – Agreed to by the applicant
Route(s) of administration	Adequate	Topical gel 14-NOV-2023 – Agreed to by the applicant
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Back Panel Revise to: After mixing, each gram of ZELSUVMI contains berdazimer 103 mg (equivalent to 109 mg berdazimer sodium) 14-NOV-2023 – Agreed to by the applicant
Net contents (e.g., tablet count, volume of liquid)	Adequate	Revise as recommended below 14-NOV-2023 – Agreed to by the applicant
"Rx only" displayed on the principal display	Adequate	Revise as recommended below 14-NOV-2023 – Agreed to by the applicant
NDC	Adequate	Revise as recommended below 14-NOV-2023 – Agreed to by the applicant
Lot number and expiration date	Adequate	Revise as recommended below 14-NOV-2023 – Agreed to by the applicant
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Revise as recommended below 14-NOV-2023 – Agreed to by the applicant 12-DEC-2023 - Applicant was requested to add a statement regarding flammability of formulation or provide evidence the product is not flammable.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	Revise Tube B Carton and Kit Carton to include % ethanol in inactive ingredient list 12-DEC-2023 – Communicated to the applicant
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ***ADEQUATE (per revised labels provided on 13-NOV-2023 and the communication to the applicant on 12-DEC-2023 requesting %ethanol be included and statement of flammability)***

Note: DMEPA and OPQ comments have been combined to improve clarity and correctness of the carton and container labels as follows:

Container Labels, Carton Labeling and Kit Label (All)

1. In accordance with 21 CFR 201.55, the 'Direction' 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 'Do not use after 60 days' statement should be revised (see below) and relocated to the last sentence of the storage section:

   'Discard 60 days after removal from refrigeration.'

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

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 (instead of berdazimer) and Tube B (instead of hydrogel) 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 "(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. <u>Side panel</u>
   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 (xx%), glycerin, potassium phosphate monobasic, and purified water

4. <u>Back panel:</u>
   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 intravaginal 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:
  - [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 intravaginal 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:
  - Contains benzoic acid, carboxymethylcellulose sodium, cyclomethicone, ethanol (XX%), 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 intravaginal 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 intravaginal use.
NET WT. **17 g**

Dosing Card

The blue berdazimer strip should be renamed as Tube A and the yellow hydrogel strip should be renamed as Tube B.

Overall Assessment and Recommendation:

The Label and Labeling recommendations for NDA 217424 were communicated to OND on July 27, 2023, September 1, 2023 and December 7, 2023. The Applicant agreed to the label comments and provided updated labels on November 13, 2023. The Applicant provided revised labeling (PI) on November 13, 2023 and November 27, 2023.

On December 7, 2023, the below comments were provided to OND, who in turn communicated them to the Applicant on December 12, 2023.

For consistency with:
FDCA section 502(e)(1(A)(ii)
21 CFR 201.10(d)(2)

- **Calculate and add the % v/v of ethanol in the Tube B formulation in section 11 of the PI. This information should also appear on the Tube B Carton, and the Kit Carton.**

- **Include a flammability statement such as "Product contains alcohol and should be kept away from open flame" throughout the PI, IFU and Container Closure or provide evidence Tube A, Tube B, and the mixed gel is not flammable.**

The Labeling and Label of NDA 217424 are ADEQUATE, pending concurrence from the Applicant on the above two items communicated on December 12, 2023.

Primary Labeling Assessor Name and Date:

Caroline Strasinger, PhD

CDER/OPQ/ONDP/DNDP2

12/14/2023

Secondary Labeling Assessor Name and Date:

Julia Pinto, PhD

CDER/OPQ/ONDP/DNDP2

Appendix 1: Primary Labeling Reviewer Assessment on ethanol content in topical dosage forms and the Recommendation from PQL

The primary reviewer raised several concerns regarding the inclusion of the quantitative amount of alcohol (i.e., ethanol or dehydrated alcohol) in topical dosage forms including but not limited to:

1) differing interpretation of the FDCA and CFR 201.10(d)(2) in that listing of the quantitative alcohol does not apply to products where alcohol is not the active ingredient or where the dosage form is not a parenteral (i.e., per CFR 201.100, only parenteral formulations list quantitative amounts of in actives).

2) historically only a few topical formulations have included the % alcohol. A quick survey by the reviewer showed only 4 of 10 topical products containing ethanol have previously listed the % ethanol in the formulation.

3) the concern that prominently listing the high percentage of alcohol (often exceeding the content of beer, wine, and liquor), particularly in topical dosage forms which range from 10-92%, will attract abuse and misuse by teens or others.

PQL considered the above information and maintained the recommendation that the %v/v alcohol (meaning ethanol or dehydrated alcohol and not isopropyl alcohol) should be included in the PI, and Container Closure for ALL dosage forms, and not just parenteral formulations or OTC Liquids. The final communication from PQL follows:

QUALITY ASSESSMENT

Strasinger, Caroline

From: Abdus-Samad, Jibril
Sent: Wednesday, December 6, 2023 5:13 PM
To: Strasinger, Caroline
Cc: PQL Mailbox; Pinto, Julia; Claffey, David
Subject: RE: ethanol content in topical products
Attachments: 1995-07-07 Ethanol labeling CDER LNC.pdf; 2018-09-20_EMA information-package-leaflet-regarding-ethanol-used-excipient-medicinal-products-human-use_en.pdf

Hi Caroline,
Thank you for our discussion earlier. Here is PQL recommendation.

1. For DPs that contain alcohol (i.e., ethanol), the label must include the name and amount in % v/v. We acknowledge there have been some inconsistencies in applying the statute and regulation for some DPs. However, this is a consistent recommendation from CDER/OPQ/OPPQ/COSS PQL Team, OGD/Division of Labeling Review, and former CDER Labeling and Nomenclature Committee.
    a. FDCA section 502(e)(1(A)(ii)
    b. 21 CFR 201.10(d)(2)
    c. Additional background information (attached)
        i. CDER Labeling and Nomenclature Committee document noting when alcohol should not be labeled (when less than 0.1%) from 1995-Jul-07
        ii. EMA: Committee for Medicinal Products for Human Use (CHMP): Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use, 2018-Sep

2. FDCA states "unless the *label* bears..." which means the container label. Requirements for the container label must also appear on the carton and PI (see FDCA 201(k)).
    a. Add "alcohol *X* % (v/v)" within the listing of ingredients on the container labels (if space permits), carton labeling, and within PI section 11.
        i. If the container label is to small and does not include the list of ingredients, then the carton labeling is sufficient.

3. OPPQ (Labeling SME and Reg Counsel) will meet internally to develop a policy document (e.g., work-aid) for Labeling Requirements for Alcohol.

4. Just wondering, if the labels and labeling have a flammable warning considering the amount of ethanol and IPA.

5. References
    FDCA section 502(e)(1(A)(ii)

(e)(1)(A) If it is a drug, unless its label bears, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula)—
(i) the established name (as defined in subparagraph (3)) of the drug, if there is such a name;
(ii) the established name and quantity or, if determined to be appropriate by the Secretary, the proportion of each active ingredient, including the quantity, kind, and proportion of any alcohol, and also including whether active or not the established name and quantity or if determined to be appropriate by the Secretary, the proportion of any bromides, ether, chloroform, acetanilide, acetophenetidin, amidopyrine, antipyrine, atropine, hyoscine, hyoscyamine, arsenic, digitalis, digitalis glucosides, mercury, ouabain, strophanthin, strychnine, thyroid, or any derivative or preparation of any such substances, contained therein, except that the requirement for stating the quantity of the active ingredients, other than the quantity of those specifically named in this subclause, shall not apply to nonprescription drugs not intended for human use; and

21 CFR 201.10(d)(2)

d)
(1) If the drug is in tablet or capsule form or other unit dosage form, any statement of the quantity of an ingredient contained therein shall express the quantity of such ingredient in each such unit. If the drug is not in unit dosage form, any statement of the quantity of an ingredient contained therein shall express the amount of such ingredient in a specified unit of weight or measure of the drug, or the percentage of such ingredient in such drug. Such statements shall be in terms that are informative to licensed practitioners, in the case of a prescription drug, and to the layman, in the case of a nonprescription drug.
(2) A statement of the percentage of an ingredient in a drug shall, if the term *percent* is used without qualification, mean percent weight-in-weight, if the ingredient and the drug are both solids, or if the ingredient is a liquid and the drug is a solid; percent weight in volume at 68 °F. (20 °C.), if the ingredient is a solid and the drug is a liquid; and percent volume in volume at 68 °F. (20 °C.), if both the ingredient and the drug are liquids, except that alcohol shall be stated in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C.).

FDCA section 201(k)

(k) The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

Thanks,
Jibril

Caroline Strasinger

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Julia Pinto

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BIOPHARMACEUTICS

Product Background:

NDA: NDA 217424-ORIG-1

Drug Product Name / Strength: Berdazimer gel/10.3%

Indication: Treatment of molluscum contagiosum

Route of Administration: Topical

Applicant Name: Novan, Inc.

Review Recommendation: The submission is **ADEQUATE** from Biopharmaceutics perspective.

Review Summary:

SB206 (berdazimer) gel is a mixture of two components, an active (b) (4) gel containing berdazimer sodium (the API) and a hydrogel component. Upon mixture, the hydrogel component triggers decomposition of the API in the active gel component to release nitric oxide (NO) for therapeutic effect. Berdazimer sodium (NVN1000) is an NME. This NDA was submitted via a 505(b)(1) pathway.

In Vitro Release Test (IVRT) and Acceptance Criteria: ADEQUATE

The Applicant developed and validated an IVRT method that monitors the release rate of NO from SB206 gel. This method involves direct monitoring of berdazimer sodium decomposition in the admixture. (b) (4) To quantify changes in release over time, samples are aliquoted from the sample beaker at specified timepoints. The proposed IVRT method is acceptable based on the totality of data provided including justification of the selected method conditions, discriminating ability of the method, and low variability of the generated data.

The following IVRT acceptance criteria is recommended to be approved for both release and stability.

Average slope (decomposition rate): (b) (4)
Average assay (%w/w berdazimer at 20 minutes): (b) (4)

It is noted that the proposed acceptance criteria for slope and assay were set considering a mean ± 5σ approach, which is wider than the standard 3σ limits. After multiple communications, the Applicant agreed to submit the future batch data in the next annual report and if the data complies to ± 3σ range, the specification will be revised accordingly.

Formulation Development and Bridging: ADEQUATE
There was no formulation change between the pivotal phase 3 study batch and the commercial batch. The Phase 3 studies were all conducted with the To-Be-Marketed (TBM) formulation and strength (i.e., SB206 Gel, 10.3%).

API Manufacturing Site Change: ADEQUATE
The applicant proposed Novan Inc. (Durham site) as the commercial drug substance manufacturing site. Novan site (Morrisville, NC) is the current drug substance manufacturing site. The applicant also proposed Orion Pharma (Turku, Finland) as the commercial drug product manufacturing site. In response to an IR, the Applicant submitted comparative IVRT data for the SB206 gel manufactured at Orion Pharma using the drug substance from the current manufacturing site (pre-change) and the drug substance from the proposed commercial manufacturing site (post-change). This reviewer confirmed that the 90% confidence intervals for the post-change batch and the pre-change batch meet the equivalence acceptance criteria of 75% to 133.33% in accordance with the FDA's SUPAC-SS guidance. Hence, the release profiles of the batches manufactured at Orion site using pre-change and post-change APIs are similar.

Biowaiver Request: Not requested
Only one strength is developed.

List of Submissions being reviewed:
Sequence 0001, 0010, 0018, 0021, 0022

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

BCS Designation

Reviewer's Assessment: The Applicant did not make a BCS Class designation claim. Since the proposed product is a topical system, BCS classification is not applicable.

Solubility:
Per the Applicant, intact berdazimer sodium is insoluble in all solvents evaluated and is susceptible to hydrolysis (i.e., digestion/breakdown of the polymer structure) in aqueous solutions.

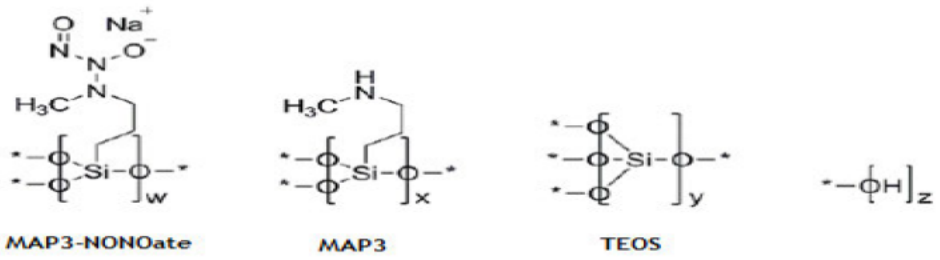
Permeability: N/A

Dissolution: Please see in the sections below.

1. Description of the Drug Product

SB206 is a mixture of two components, an active (b) (4) gel containing berdazimer sodium (the API) and a hydrogel component. Upon mixture, the hydrogel component triggers decomposition of the API in the active gel component to release nitric oxide (NO).

Figure 1: Polymeric Structure of Berdazimer Drug Substance



Berdazimer sodium

* Denotes shared oxygen atom between bonded constituents; resulting bonds are Si-O-Si or Si-OH

w : x : y : z = 3 : 1 : 6 : ~5

(b) (4)

2. Composition of proposed drug product

The composition of the active gel component and hydrogel component of SB206 Gel are provided in the tables below. The calculated composition of SB206 Gel after mixing 0.5 mL of active gel (b) (4) with 0.5 mL of hydrogel (b) (4) is provided in Table 3.

Table 1: Composition of Active Gel Component of SB206 Gel

Ingredient	Quality Standard	Function	%w/w	mg/dose[2]
Berdazimer Sodium	In-House	Active Pharmaceutical Ingredient	(b) (4)	
Isopropyl Alcohol	USP and Ph. Eur.			
Hexylene Glycol	NF			
Cyclomethicone	NF			
Hydroxypropyl Cellulose	NF			
Total				

NF – National Formulary, Ph. Eur. – European Pharmacopoeia, USP – United States Pharmacopeia

(b) (4)

Table 2: Composition of Hydrogel Component of SB206 Gel

Ingredient	Quality Standard	Function	%w/w	mg/dose[1]
Purified Water	USP			(b) (4)
Monobasic Potassium Phosphate	NF			
(b) (4) (Ethanol, (b) (4)	USP and Ph. Eur.			
(b) (4)				
Cyclomethicone	NF			
Carboxymethylcellulose Sodium	USP			
Benzoic Acid	USP and Ph. Eur.			
Total				

NF – National Formulary, Ph. Eur. – European Pharmacopoeia, USP – United States Pharmacopeia, JP – Japanese Pharmacopeia

(b) (4)

Table 3: Calculated Composition of SB206 Gel

Ingredient	Quality Standard	Function	% w/w[1]	mg/dose[1]
Purified Water	USP			(b) (4)
Isopropyl Alcohol	USP and Ph. Eur.			
(b) (4) Ethanol, (b) (4)	USP and Ph. Eur.			
(b) (4)				
Hexylene Glycol	NF			
Berdazimer Sodium	In-House			
Cyclomethicone	NF			
Hydroxypropyl Cellulose	NF			
Carboxymethylcellulose Sodium	USP			
Potassium Phosphate Monobasic	NF			
Benzoic Acid	USP and Ph. Eur.			
Total				

NF – National Formulary, Ph. Eur. – European Pharmacopoeia, USP – United States Pharmacopeia, JP – Japanese Pharmacopeia

(b) (4)

[2] Equivalent to 10.3% w/w berdazimer

3. IVRT method and acceptance criteria

The Applicant initially developed a conventional IVRT method for SB206 (b) (4)

However, the method presented significant analytical challenges resulting in high variability for multiple batches during the development and clinical stages; therefore, an alternative method was developed that more accurately monitors the release rate of NO from SB206 gel and is more robust and repeatable compared to the conventional IVRT method. This method involves *direct* monitoring of berdazimer sodium decomposition in the admixture. Figure below illustrates the different approaches in analyte selection for the proposed method compared to the conventional method.

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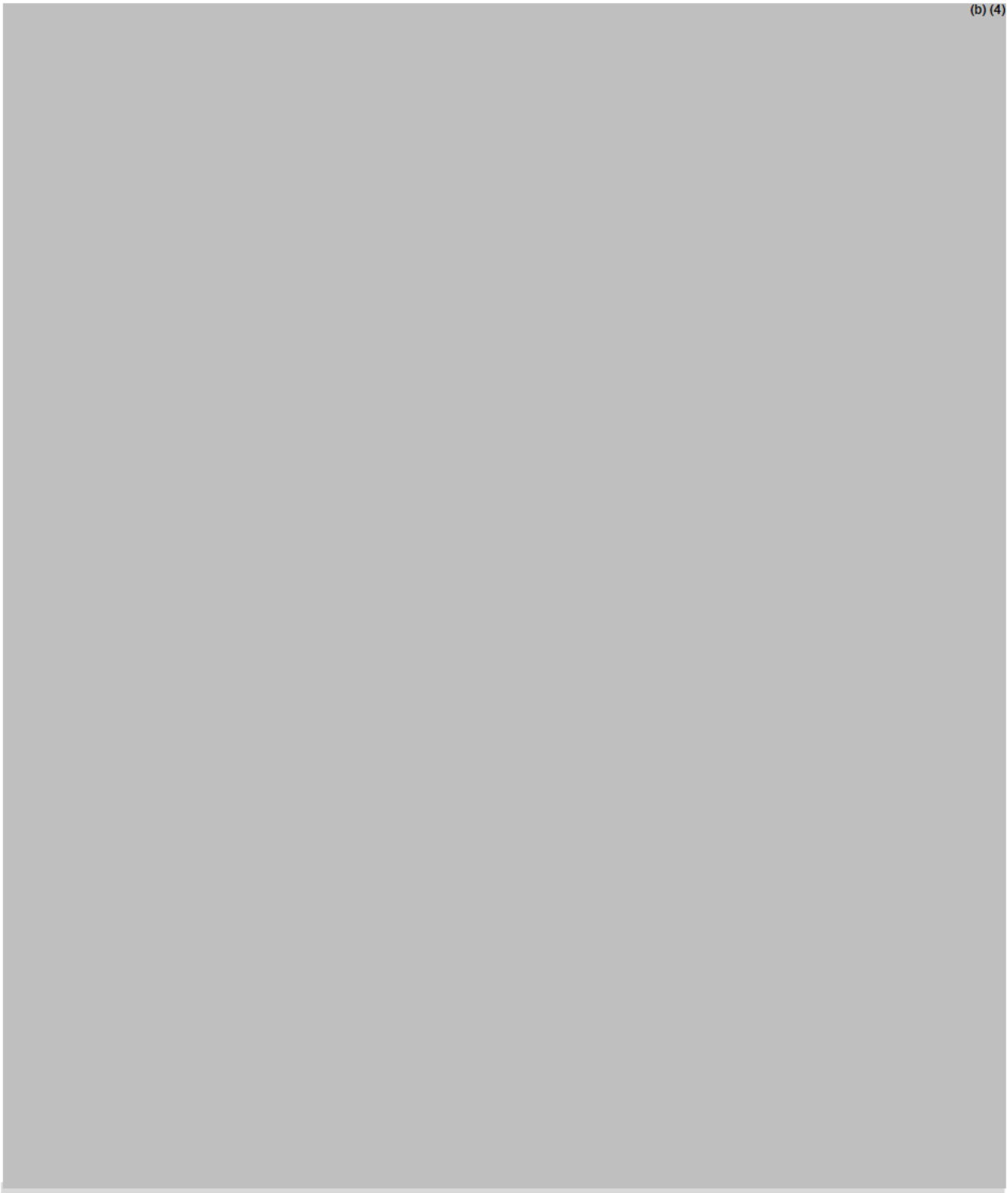
(b) (4)



Discriminating ability of the IVRT method

The Applicant conducted additional studies to show discriminating ability towards the critical material attributes (CMAs), critical process parameters (CPPs), and critical formulation variables (CFVs). The most relevant CMAs, CPPs, and CFVs were identified, and batches were manufactured at the nominal target ranges and with deliberate variations. To demonstrate the discriminating ability of the method, the release profiles of the target (reference) and the changed

(test) batches for each attribute were obtained and compared using the Mann-Whitney U test described in USP <1724> "Semisolid Drug Products – Performance Tests".

A summary of these studies is provided below. The details can be found in the below link: \\CDSESUB1\EVSPROD\nda217424\0001\m3\32-body-data\32r-reg-info\methodvalidationpackageorreports\ivrt-supplemental-report.pdf

Table 5 summarizes the statistical test data obtained for the batches tested, demonstrating the ability of the method to discriminate release rates and/or %w/w values.

Table 5: Summary of Statistical Test Data for All Parameters Evaluated

Active Gel Variation		Statistical Sameness	
		Release Rate	%w/w Berdazimer
(b) (4)		No	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Statistical Sameness	
		Release Rate	%w/w Berdazimer
		Yes	Yes
		No	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		Yes	Yes
		No	No
		Yes	No
		Yes	No
		Yes	Yes
		Yes	Yes
		Yes	Yes

Table 6: Active Gel CMAs/CPPs/CFVs Affecting In Vitro Drug Release

Category	Parameter	Variation
CFV	(b) (4)	

The data obtained for the admixtures with the (b) (4) variation for the active gel were shown to be statistically dissimilar (figure below) and two out of the six preparations did not meet the acceptance criterion for %w/w berdazimer at 20 minutes. Conversely, the (b) (4) variation admixtures were shown to be statistically similar, and all results were within specification.

Figure 11: Release Profiles for Active Gel (b) (4) Concentration Variation

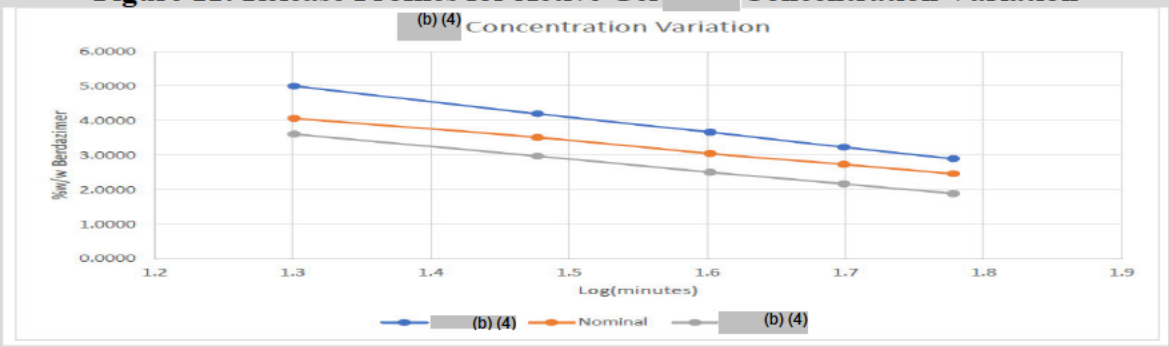
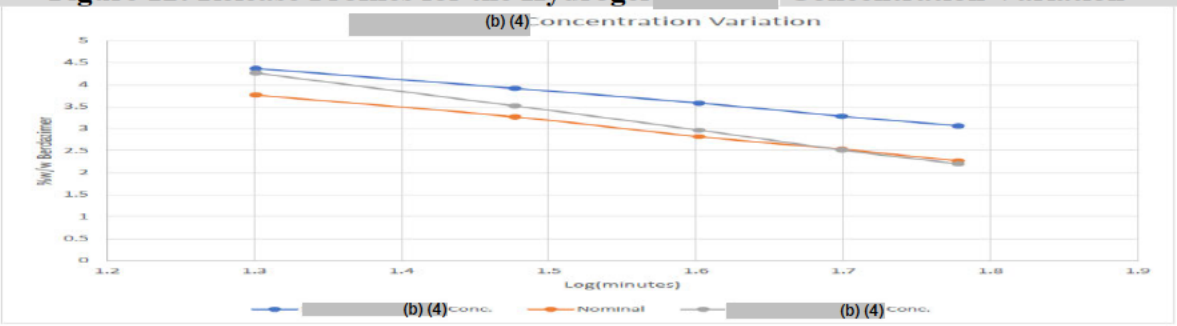


Table 7: Hydrogel CMAs/CPPs/CFVs Affecting In Vitro Drug Release

Category	Parameter	Variation
CFV	(b) (4)	

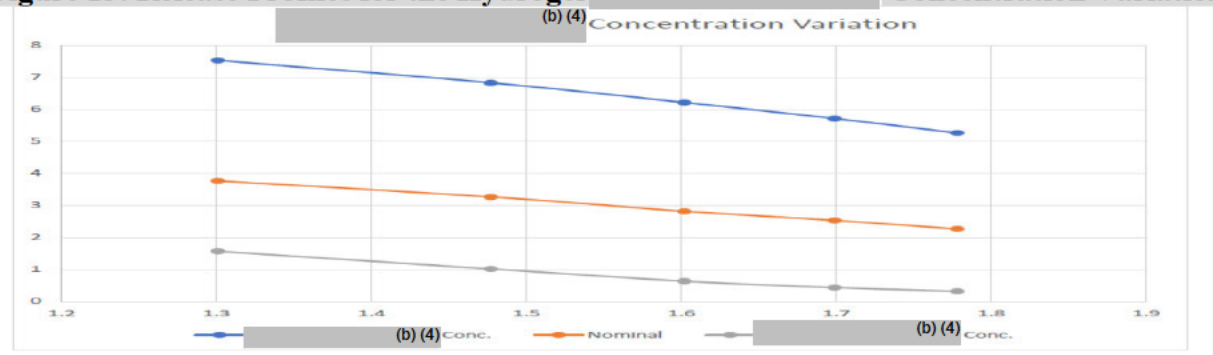
The data obtained for the admixtures with the (b) (4) variation for the hydrogel were shown to be statistically dissimilar for the slope values (figure below). Conversely, the (b) (4) variation admixtures were shown to be statistically similar, and all results were within specification.

Figure 12: Release Profiles for the Hydrogel (b) (4) Concentration Variation



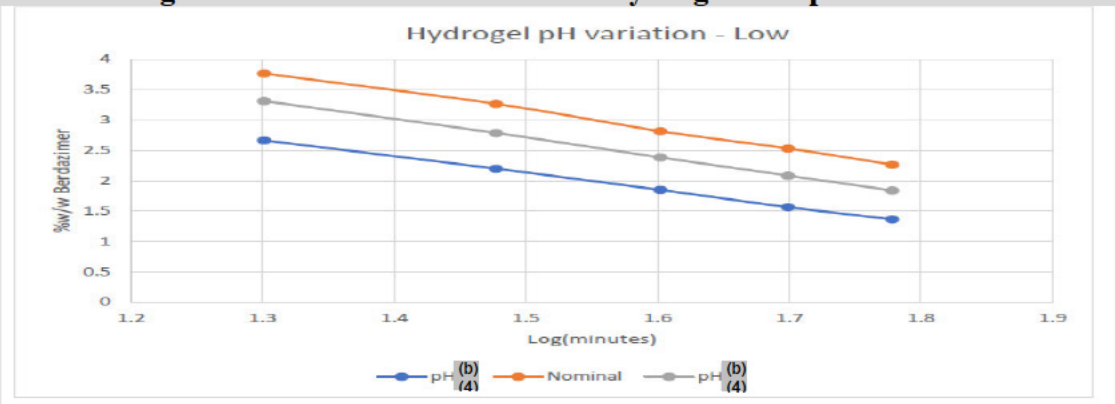
The data obtained for the admixtures with the hydrogel (b) (4) variations (figure below) were shown to be statistically different compared to the target batch and did not meet the proposed specification for the %w/w values.

Figure 13: Release Profiles for the Hydrogel (b) (4) Concentration Variation



The data obtained for the admixtures with the hydrogel at pH (b) (4) is shown to be statistically dissimilar for the %w/w values (figure below). The data obtained for the admixture with the hydrogel at pH (b) (4) is statistically similar compared to the reference which supports the low end of the proposed commercial specification for the pH of the hydrogel (b) (4)

Figure 14: Release Profiles for the Hydrogel Low pH Variation



The method was also shown to discriminate release rates from formulations manufactured at different strengths during the analytical validation as shown below in IVRT Validation Report: \\CDSESUB1\EVSPROD\nda217424\0001\m3\32-body-data\32r-reg-info\methodvalidationpackageorreports\ivrt-validaiton-report.pdf

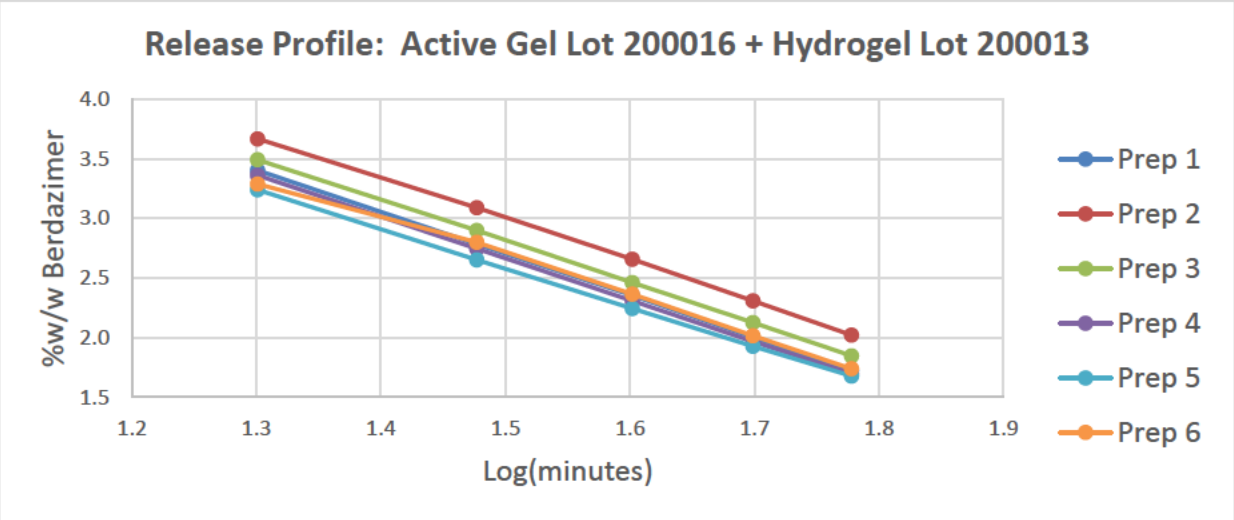
In vitro release acceptance criteria

The Applicant proposed following IVRT specification for both release and stability:

Average slope (decomposition rate): (b) (4)
Average slope: %RSD of (b) (4)
Average assay (%w/w berdazimer at 20 minutes): (b) (4)
Average assay: %RSD of (b) (4)

In response to an IR (IR1.2 in Appendix 1), the Applicant provided individual drug release data for the clinical and registration/stability batches. The in vitro drug release profiles (n=6) of one lot (Active Gel Lot 200016 + Hydrogel Lot 200013) are presented in the figure below.

Figure 15: In Vitro Drug Release Profiles of Active Gel Lot 200016 + Hydrogel Lot 200013



It is noted that the proposed acceptance criteria for slope and assay were set wider than the standard 3σ limits. The Applicant was requested to provide data to support the minimum and maximum values of the proposed slope and assay (IR2 in Appendix 1). In the response, the Applicant noted that the proposed acceptance criteria were set considering a ± 5σ approach based on the obtained results in table below as it's a newly developed method and to account for anticipated analyst, test site, and equipment variability. The %RSD of (b) (4) was implemented as it is the traditional acceptance criterion for a conventional IVRT method.

Table 8: Batch Results Used for IVRT in SB206 Gel Acceptance Criteria

Active Gel/Hydrogel Batch Pairing	IVRT Average Slope (Decomposition Rate) (n=6)	%RSD	IVRT Average Assay in % w/w at 20 minutes (n=6)	%RSD
200014/200011	(b) (4)			
200015/200012				
200016/200013				
190043/190032				
190044/190034				
220012/2088282				
220013/2088282				
2082052/2088269				
2082069/2088281				
2092072/2088282				
Average	**-3.3**	**NA**	**3.2**	**NA**
Standard deviation (σ)	**0.24**	**NA**	**0.44**	**NA**
+5σ	**-2.1**	**NA**	**5.4**	**NA**
-5σ	**-4.5**	**NA**	**1.0**	**NA**

NA – Not Applicable

It is noted that with ± 3σ approach, the slope range spans between (b) (4) and the provided data supports this range. RSD of all batches are low and supports consistencies among the batches. Therefore, it was recommended to follow a ± 3σ approach (IR3 in Appendix 1). The applicant noted in the response that the current proposed specification considering a ± 5σ approach does not impact product quality and supports clinical safety and efficacy of the drug product. Additionally, the ± 5σ approach is supported by the robustness experiments performed during the method validation that demonstrated statistical sameness using the Mann Whitney U Test with results exceeding a ± 3σ range. The Applicant proposed to implement an alert limit for IVRT results that fall outside the (b) (4) range but within the current proposed specification range of (b) (4). Upon notification of a result exceeding the alert limit but within the specification, an out of trend (OOT) investigation will be performed and documented in the batch data. Batches meeting the specification but exceeding the alert limit may still be deemed suitable for commercial use pending the outcome of the OOT investigation. The Applicant also committed to re-evaluating the IVRT specification with additional commercial batch data during the annual product reviews and if the IVRT data for a minimum of 30 batches continues to support a ± 3σ approach, the specification will be revised accordingly.

While the Applicant's justification is acceptable on an interim basis, it was recommended that they should submit IVRT data from all future batches in the next annual report. If the data from these batches demonstrate that they comply to ± 3σ range, they need to adopt that range and revise the specification accordingly. The Applicant agreed to submit the future batch data in next annual report and if the data complies to ± 3σ range, the specification will be revised accordingly.

4. Formulation development and bridging

There was no formulation change between the pivotal phase 3 study batch and the commercial batch. The Phase 3 studies were all conducted with the TBM formulation and strength (i.e., SB206 Gel, 10.3%).

5. Drug substance manufacturing site change

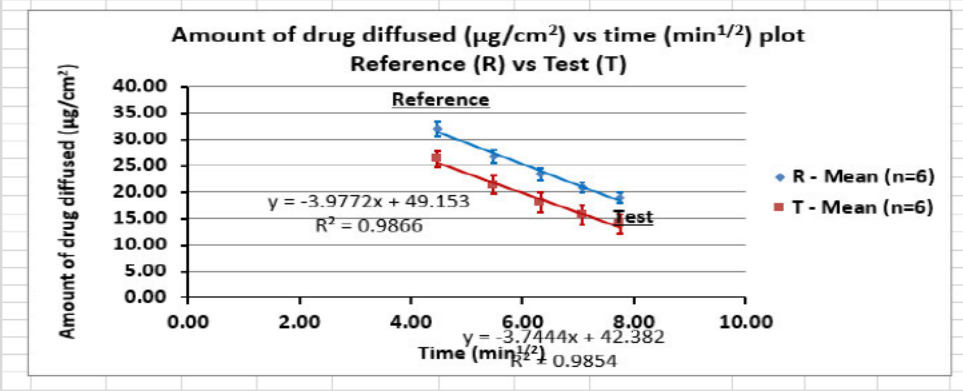
The applicant proposed Novan Inc. (Durham site) as the commercial drug substance manufacturing site. Novan site (Morrisville, NC, USA) is the current drug substance manufacturing site. The applicant also proposed Orion Pharma (Turku, Finland) as the proposed commercial drug product manufacturing site. Phase 3 and Primary registration batches were manufactured at current Novan site (Morrisville, NC, USA).

The Applicant did not provide comparative IVRT data for the SB206 gel manufactured at Orion Pharma using the drug substance from the current manufacturing site (pre-change) and the drug substance from the proposed commercial manufacturing site (post-change) in the original submission. Hence, the Applicant was requested to submit all the generated data (IR1.1 in Appendix). In response to the IR, the Applicant submitted IVRT data and profiles for the SB206 gel manufactured at Orion with both pre-change and post-change APIs as follows:

Table 9: IVRT File Names for SB206 Gel Drug Product Manufactured at Orion Pharma

Drug Product Batch	Drug Substance Mfg Site Change	MS Excel Data File Name
2127635-2126911	Post-Change	IVRT Replacement Method Post Change 2127635-2126911
2127946-2126911	Post-Change	IVRT Replacement Method Post Change 2127946-2126911
2082052-2088269	Pre-Change	IVRT Replacement Method Pre Change 2082052-2088269
2082069-2088281	Pre-Change	IVRT Replacement Method Pre Change 2082069-2088281
2092072-2088282	Pre-Change	IVRT Replacement Method Pre Change 2092072-2088282

The Applicant assessed IVRT data generated at release for drug product batches 2082052-2088269 (pre-change) and 2127946-2126911 (post-change) for sameness using the Mann-Whitney U test described in USP <1724> "Semisolid Drug Products – Performance Tests". This reviewer confirmed that the 90% confidence intervals for the post-change batch and the pre-change batch meet the equivalence acceptance criteria of 75% to 133.33% in accordance with the FDA's SUPAC-SS guidance. Hence, the release profiles (see the figure below) of the batches manufactured at Orion site using pre-change and post-change APIs are similar.



Conclusion: The submission is **ADEQUATE** from Biopharmaceutics perspective.

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Topical gel for the treatment of molluscum contagiosum
NDA Number	217424
Assessment Cycle Number	MR01
Drug Product Name/ Strength	SB206 [berdazimer] Gel 10.3%
Route of Administration	Topical
Applicant Name	Novan, Inc
Therapeutic Classification/ OND Division	OND/OII/DDD
Manufacturing Site	Orion Corporation, Orion Pharma Tengströminkatu 8 Turku, FI-20380 Finland FEI: 3003743938
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The proposed drug product consists of two gel components in separate multi-dose tubes for topical administration. The active gel component contains the API in an alcohol-based formulation. The hydrogel component is an aqueous gel (b) (4) Both gels are filled into aluminum tubes.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 Original Submission	5 January 2023
0009 Revised Patient Labeling	22 March 2023
0016 Quality IR Response	26 June 2023
0027 CMC Amendment	30 October 2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: N/A

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The drug product is non-sterile. The drug substance will not be reviewed here.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(eCTD 0001 Section 3.2.P.1 description-and-composition.pdf)

Description of drug product – The SB206 Gel Drug Product consists of the active gel and the hydrogel in separate containers co-packaged within the final container closure system. The active gel component of SB206 Gel is a white to off-white opaque gel in an aluminum tube with a white reverse-taper puncture tip (RTPT) cap. It is an isopropyl alcohol/hydroxypropyl cellulose-based gel and contains the berdazimer sodium drug substance (b) (4) The hydrogel component of SB206 Gel is a white to off-white translucent to opaque gel in an aluminum tube with a white RTPT cap. It is a carboxymethylcellulose sodium-based gel buffered with potassium phosphate (b) (4) At the point of use, equal volumes of the active gel and the hydrogel are dispensed and mixed together according to instructions. Once mixed, the hydrogel reacts with the drug substance (berdazimer sodium) in the active gel to release nitric oxide gas (NO). The DP is intended to treat the viral infection Molluscum Contagiosum in adult and pediatric patients (b) (4) of age and older.

Drug product composition –

SB206 Gel component	Ingredient	Function	Concentration (%w/w)
Active Gel	Berdazimer sodium	Active Ingredient	(b) (4)
	Isopropyl alcohol		(b) (4)
	Hexylene glycol		
	Cyclomethicone		
	Hydroxypropyl cellulose		
Hydrogel	Purified water		
	Monobasic potassium phosphate		
	(b) (4) ethanol, (b) (4)		
	(b) (4)		
	Cyclomethicone		
	Carboxymethylcellulose sodium		
	Benzoic acid		

Description of container closure system – Both gel components are filled in the same container closure system:

Component	Description	Manufacturer
Tube		(b) (4)
Cap		

Assessment: *Adequate*

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbial control of the product.

(b) (4)

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CAROLINE STRASINGER
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