CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217424Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	217424
PDUFA Goal Date	January 05, 2024
Nexus TTT #	2023-3360
Reviewer Name(s)	Carla Darling, PharmD, BCPS
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Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 5, 2023
Subject	Evaluation of Need for a REMS
Established Name	Berdazimer 10.3% topical gel
Trade Name	Zelsuvmi
Name of Applicant	Novan, Inc.
Therapeutic Class	Nitric oxide releasing agent
Formulation(s)	Topical gel
Dosing Regimen	Mix equal amounts of Tube A and Tube B together and immediately apply an even thin layer once daily to each molluscum lesion for up to 12 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Zelsuvmi (berdazimer) topical gel is necessary to ensure the benefits outweigh its risks. Novan, Incorporated (Applicant) submitted a New Drug Application (NDA) 217424 for berdazimer with the proposed indication (b) (4) (b) (4) (b) (4) "Zelsuvmi is indicated for the topical treatment of molluscum contagiosum in adults and pediatric patients 1 year of age and older." The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Dermatology and Dentistry (DDD) agree that a REMS is not necessary to ensure the benefits of berdazimer outweigh its risks. Data from two vehicle-controlled phase 3 trials provided evidence of effectiveness of berdazimer for the topical treatment of MC in adult and pediatric patients 1 year of age and older. One trial showed statistically significant improvements in clearance of all treatable MC lesions at week 12. The second trial did not reach the nominal statistical significance level of 0.05%; however, the DDD determined that the results for this trial were persuasive and concluded that the two trials provided substantial evidence of effectiveness. The main risk associated berdazimer is allergic contact dermatitis. This risk is included in the warnings and precautions section of the prescribing information. Likely prescribers of berdazimer should be familiar with monitoring and management of this risk. Based on the safety and efficacy demonstrated in clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Zelsuvmi (berdazimer) topical gel is necessary to ensure the benefits outweigh its risks. Novan, Incorporated (Applicant) submitted a New Drug Application (NDA) 217424 for berdazimer gel with the proposed indication for the topical treatment of molluscum contagiosum (MC) in adult and pediatric patients (b) (4) of age and older. This application is under review in the Division of Dermatology and Dentistry (DDD). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Berdazimer, a NME,[a] is a Nitric oxide (NO) releasing agent, proposed for the topical treatment of MC in adult and pediatric patients 1 year of age and older.[1] The specific mechanism of action in MC is not well

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

known. Berdazimer is proposed as a 10.3% topical gel applied once daily to each molluscum lesion for up to 12 weeks.[1, b] Berdazimer is supplied as two tubes, Tube A, which contains active berdazimer (b) (4) gel and Tube B, which contains inactive hydrogel. Equal amounts of each tube are mixed together prior to immediate application to each lesion. Berdazimer is intended for administration by patients or caregivers in the outpatient setting.[2] Berdazimer is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217424relevant to this review:

- 01/05/2023: NDA 217424 submission for the topical treatment of MC in adult and pediatric patients (b) (4) of age and older received.
- 06/21/2023: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no major clinical safety issues have been identified, and a REMS for berdazimer will likely not be required.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

MC is a common and highly transmissible viral skin infection caused by poxvirus (molluscum contagiosum virus) characterized by small (2 to 5 mm in diameter), skin-colored, dome-shaped lesions with central umbilication.[3,4] Lesions spontaneously resolve without scarring after approximately two months and may appear anywhere on the body with the exception of the palms and soles.[3,4, c] In most cases, the infection completely resolves in 6 to 12 months but sometimes can persist for up to 5 years.[3] Infections can include localized dermatitis with or without pruritus around the lesions and inflamed lesions.[3] MC is most commonly seen in children with a worldwide prevalence of 5.1 to 11.5% and an overall incidence rate in children of 12-14 episodes per 1000 person years.[5, d] While the incidence in the United states is largely unknown, a 2009 study of American Indians and Alaskan Natives in the United States estimated an incidence rate of 2.01 per 1000 people.[6]

3.2. Description of Current Treatment Options

MC lesions are self-resolving; however, treatment of lesions may be used to limit the spread of lesions to other sites and to other people.[3,7,8] Ycanth (cantharadin) is the only Food and Drug Administration (FDA) approved treatment for MC in adult and pediatric patients 2 years of age and older.[9] Ycanth, approved on July 24, 2023, is a topical cantharidin 0.7% solution prepared as a combined drug-device product that can be applied directly to individual MC lesions. Ycanth is administered to patients only by

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*
[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*
[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

health care providers as a single application and may be repeated every 3 weeks as needed. The risks associated with cantharidin include local skin reactions, flammability, and life threatening or fatal toxicities can occur if administered orally. The risks associated with inappropriate administration are described in the Warnings and Precautions section of the Ycanth Prescribing Information.

4. Benefit Assessment

The efficacy and safety of berdazimer for the treatment of MC was evaluated in three phase 3 randomized, double-blind, placebo-controlled trials, NI-MC301 (NCT03927716), NI-MC302 (NCT03927703), and NI-MC304 (NCT 04535531). The three phase 3 trials were similar in design with a 12-week duration followed by a 12-week safety follow up period. Eligible patients were randomized to vehicle or berdazimer topically applied to each lesion daily. The primary endpoint was proportion of subjects with complete clearance of all treatable MC lesions at Week 12. The secondary endpoint was proportion of subjects with complete clearance of all treatable MC lesions at Week 8. Trial NI-MC304 was the pivotal trial supporting the effectiveness of berdazimer and the other two trials, NI-MC302 and NI-MC301 were proposed to provide supportive evidence.

The pivotal trial, NI-MC304 enrolled 891 subjects, 6 months of age and older with between 3 to 70 lesions at baseline. Berdazimer demonstrated statistically significant superiority over vehicle for complete clearance of all MC lesions at week 12 with a treatment difference (TD) of 12.8% ($p<0.0012$).[10] Trial NI-MC302 marginally failed to meet the primary endpoint with a TD of 9.2% ($p=0.0510$) and the TD of 4.3% in trial NI-MC301 ($p=0.3637$) failed to meet the primary endpoint.[10] For the key secondary endpoint, efficacy of berdazimer compared to the vehicle gel was demonstrated in the pivotal trial NI-MC304 ($p=0.0012$) and in trial NI-MC302 ($p=0.0114$); however, the statistical significance was not achieved in trial NI-MC301 ($p=0.1801$).[10]

The Division of Dermatology and Dentistry (DDD) determined that trials NI-MC301, NI-MC302, and NI-MC304 were adequate and well-controlled (AWC) investigations with adequate data for assessment of efficacy and safety. However, trials NI-MC302 and NI-MC301 did not meet the prespecified statistical significance levels, therefore the DDD solicited input from the Medical Policy and Program Review Council (MPPRC) regarding the approvability of berdazimer gel and whether Trials NI-MC302 and NI-MC304 are adequate to demonstrate substantial evidence of effectiveness (SEE). The MPPRC considered that trial NI-MC304 demonstrated a significant treatment effect; trial NI-MC302 had a robust finding, particularly related to a continuous analysis of the total lesion count but failed based on conservative statistical responder (binary) analysis; and trial NI-MC301 also suggested drug effectiveness, even though it demonstrated a formally negative trial result. Overall, the MPPRC considered trials NI-MC302 and NI-MC304 as two AWC trials that provide SEE.

The DDD concluded that the Applicant provided substantial evidence of effectiveness for berdazimer for the treatment of MC.[11, e] See the Multi-Disciplinary Review and Evaluation for berdazimer gel for more details regarding the DDD's conclusions for evidence of effectiveness.

5. Risk Assessment & Safe-Use Conditions

The safety analysis for berdazimer consists of pooled data from randomized subjects who received at least 1 study drug application from the three phase 3 trials, NI-MC301, NI-MC302, and NI-MC304. No long-term safety study was conducted for this drug product. The pooled data from the three phase 3 trials (n=1596) includes 680 subjects who received the vehicle and 916 subjects who received berdazimer. The most common adverse events in subjects receiving berdazimer included application site reactions.[1] The majority of adverse events were mild to moderate in severity.[12]

Allergic contact dermatitis was a submission-specific safety issue that was reported as a treatment emergent adverse event by 4.9% of subjects receiving berdazimer compared to 0.7% of subjects receiving vehicle.[11, f]

No deaths were reported during phase 3 trials. One (1) subject treated with berdazimer had a serious adverse reaction[g] (SAR) of cellulitis (not near study drug application site). Study drug was interrupted, and the subject was treated with clindamycin. The review team concluded that this adverse event did not appear to be treatment related.[11]

Overall, the review team concluded that based on the safety data for treatment of MC, no safety signals were identified.[11] Proposed labeling includes the risk of application site reactions in section 5, warnings and precautions of the prescribing information.[1]

6. Expected Postmarket Use

The likely prescribers of berdazimer include dermatologists, primary care physicians, and pediatricians. Berdazimer is intended for self-administration by the patient or caregiver in the outpatient setting.[2] If approved, berdazimer will be the second FDA approved drug product for the treatment of MC. The safety risks including application site reactions are likely known to these prescribers.

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[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for berdazimer beyond routine pharmacovigilance and labeling.[13]

8. Discussion of Need for a REMS

The review team recommends approval of berdazimer on the basis of the efficacy and safety information currently available.[11]

Berdazimer is a nitric oxide releasing agent for treatment of MC. MC is a common, self-limiting, localized infection of the skin in children and adults. Benefits of treatment include prevention of disease transmission and spread, alleviating any discomfort or cosmetic concerns, and prevention of secondary infections. While there is one FDA treatment recently approved for the treatment of MC that is administered by a healthcare provider, there is an unmet need for self-administered treatment options. Berdazimer offers an effective self-administered treatment option for MC. The use of berdazimer was found statistically superior to vehicle in achieving complete clearance of all treatable MC lesions by Week 12 in the pivotal phase 3 trial and a second phase 3 trial that marginally failed to meet statistical significance provided persuasive results. (b) (4)

the indication was revised to "the topical treatment of molluscum contagiosum in adults and pediatric patients 1 year of age and older."[1] The Division of Dermatology and Dentistry determined that there is substantial evidence of effectiveness for berdazimer for the treatment of MC with an acceptable safety profile.[11]

Berdazimer is associated with a risk of application site reactions. This risk will be communicated through the Warnings and Precautions section of the labeling. As the risk of application site reactions are not serious safety risks, this reviewer concluded that based on the available safety information, a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for berdazimer to ensure the benefits outweigh the risks. At the time of this review, labeling negotiations were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should the Division of Dermatology and Dentistry have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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