CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212905Orig1s000

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	212905
PDUFA Goal Date	July 23, 2023
Nexus TTT #	2023-3476
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 19, 2023
Subject	Evaluation of Need for a REMS
Established Name	Cantharidin 0.7% topical solution
Trade Name	Ycanth
Name of Applicant	Verrica Pharmaceuticals, Inc
Therapeutic Class	Vesicant
Formulation(s)	Topical solution
Dosing Regimen	Apply topically as a single application to cover each lesion. Use no more than two applicators during a single treatment session. Remove with soap and water 24 hours after treatment. Administer every 3 weeks as needed.

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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 Ycanth (cantharidin 0.7%) topical solution is necessary to ensure the benefits outweigh its risks. Verrica Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 212905 on September 13, 2019 for the treatment of molluscum contagiosum. The Agency has issued three Complete Response (CR) letters for cantharidin which included device and various product quality deficiencies, the most recent letter was issued on May 23, 2022. Previous DRM REMS determinations were deferred. A class 2 resubmission was submitted on January 23, 2023 which is the subject of this review.

While cantharidin is available in the United States for use in compounding, Ycanth is being proposed as a drug-device combination. Cantharidin is for topical use only and intended to be administered by a healthcare provider. The risks associated with cantharidin include local skin reactions, flammability, and serious adverse events associated with inappropriate administration.

DRM and the Division of Dermatology and Dentistry (DDD) agree that a REMS is not necessary to ensure that the benefits of cantharidin outweigh its risks. The benefit of treatment for the treatment of molluscum contagiosum was demonstrated in two phase 3 pivotal trials. The indication was initially proposed as "for the treatment of molluscum contagiosum" and the Agency revised to "for the topical treatment of molluscum contagiosum in adult and pediatric patients 2 years of age and older". Although this is the first proposed drug-device combination containing cantharidin, cantharidin has been available for use in compounding for many years. The healthcare providers who are likely to prescribe, prepare, and administer cantharidin should be knowledgeable about the risks. Over the previous review cycles, the Applicant made changes to reduce the risk of accidental exposure and improve messaging on risks and appropriate preparation and administration including addition of a break tool, improvements to the user interface based on Agency recommendations, and completion of additional human factors validation studies for users, including untrained users.

Labeling will communicate instructions for preparation and administration of cantharidin for healthcare providers in Section 2, Dosage and Administration and the risks associated with inappropriate administration in Section 5, Warnings and Precautions. A patient information leaflet is proposed to communicate key risks to patients and caregivers.

Based on the available data, this reviewer concludes a REMS is not necessary to ensure the benefits outweigh the risks associated with cantharidin. Labeling is sufficient to communicate the risks and the instructions for preparation and administration.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Ycanth (cantharidin 0.7%) topical solution is necessary to ensure the

benefits outweigh its risks. Verrica Pharmaceuticals, Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 212905 on September 13, 2019 with the proposed indication for the treatment of molluscum contagiosum.[1] The Agency has issued three Complete Response (CR) Letters for cantharidin which included device and various product quality deficiencies.[2-4,a] The most recent CR Letter issued on May 23, 2022 outlined facility inspection deficiencies.[4] DRM deferred the REMS Determination for cantharidin during the previous review cycles.[5-7]

This drug product is not a new molecular entity (NME).[b] Topical cantharidin is currently commercially available as a 0.7% concentration in a base of flexible collodion for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act; however, it is not FDA approved for any indication (See Section 2.1).[8,9] Cantharidin is for topical use only and is administered by a healthcare professional. The risks associated with cantharidin include the toxicities associated with inappropriate administration, local skin reactions, flammability and serious adverse events associated with improper administration.

On January 23, 2023, the Applicant resubmitted NDA 212905 in response to the CR Letter, and is the subject of this review.[10] The Applicant did not submit any new clinical data with the resubmission.[10] The Applicant did not submit a proposed REMS and proposes to utilize labeling[c] and routine post marketing pharmacovigilance surveillance in order to address and identify any potential risks for cantharidin.[11] This application is under review in the Division of Dermatology and Dentistry (DDD).

2 Background

2.1 Product Information

Ycanth (cantharidin 0.7%) topical solution is proposed for the treatment of molluscum contagiosum. The active ingredient, cantharidin, is a naturally occurring lipophilic compound from the body fluids of the blister beetle that functions as a vesicant when topically applied to the skin. Topical cantharidin has been used by healthcare providers for the treatment of dermatologic conditions, including warts and molluscum contagiosum since the 1950s; however, it is not FDA approved for any indication in the United States.[9] It is currently available in the United States as a 0.7% concentration in a base of flexible collodion for use in compounding, and it is included on the "List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act".[8] Most compounded cantharidin preparations are available in multi-use screw top bottles and may be used for multiple treatment sessions for different patients.[12]

[a] The specific deficiencies in each of the CR letters are outlined in Section 2.2, Regulatory History but included various product quality, facilities, process (manufacturing) and human factors/device deficiencies.

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

[c] Proposed labeling includes detailed instructions for use for healthcare providers on preparing and administering cantharidin using the break tool and applicator in Section 2 of the prescribing information and a Patient Package Insert.

The Applicant proposes a single-use drug device combination product containing cantharidin 0.7% (b) (4) solution for topical administration.[13] The product will be supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. Each ampule of cantharidin contains 0.45 mL of 0.7% (b) (4) cantharidin solution. A Ycanth Break Tool (break tool) is an accessory to the applicator and was designed to assist with breaking the ampule. Cantharidin applicators will be commercialized in cartons of either 6 or 12 applicators co-packaged with 2 break tools.[14]

Compared to the available product used for compounding, the proposed product has features intended to improve safe use including single use applicator design, addition of a violet-colored dye to assist with identification of where the drug has been applied, and presence of an oral deterrent (denatonium benzoate) to discourage patients from ingesting the drug by biting or licking treated lesions.[12]

Cantharidin is intended to be administered by a healthcare provider. It is intended for topical use only and not intended for oral, mucosal, or ophthalmic use. Healthcare providers administering cantharidin will be instructed to wear gloves and eye protection during preparation and administration. The proposed dosage is as follows: apply topically as a single application to cover each lesion. Use no more than two applicators during a single treatment session. Remove with soap and water 24 hours after treatment. Cantharidin may be administered to treatable lesions every 3 weeks until all lesions are cleared.[d] In the event that cantharidin causes significant blistering, significant pain, or other adverse events, cantharidin may be removed by washing with soap and water prior to 24 hours after treatment. If cantharidin contacts any unintended surface, including healthy skin, remove by wiping with a cotton swab or gauze.

The proposed single-use drug device combination product is not available in any jurisdiction. However, cantharidin products are available in Canada and these products include a warning that they are for physician use only and should not be dispensed or prescribed for patient administration.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212905 relevant to this review:

- **09/13/2019:** A 505(b)(1) application (NDA 212905) submission was received for Ycanth (cantharidin 0.7%) topical solution.[1]
- **05/27/2020:** DMEPA completed a review evaluating the human factors validation study reports and proposed labels and labeling. The reviewer concluded the user interface of the proposed product does not support the safe and effective use of the product for the intended users, uses, and use environments. The reviewer recommended several revisions to the user interface, including device design and the IFU. Additionally, a new human factors validation study would be necessary to demonstrate the mitigations are effective.[15]

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- **06/15/2020:** DRM completed a memorandum which deferred the REMS determination until CR deficiencies were addressed.[5]
- **07/13/2020**: The Agency issued a CR Letter for Product Quality, Facilities, Process (manufacturing), and Human Factors deficiencies.[2]
- **12/23/2020:** The Agency received the Class 2 Resubmission.[13]
- **09/15/2021**: DMEPA completed a review evaluating the human factors validation study reports and proposed labels and labeling. The reviewer concluded that there is residual risk associated with exposure to the toxic solution on the skin or in the patient or user's eyes. The reviewer determined additional changes are necessary to mitigate the risks and ensure safe use of the product and that these should be evaluated in a new human factors validation study. These review team determined that the recommendations would be communicated in a General Advice Letter.[14]
- **09/16/2021:** The Agency issued a CR Letter for a Facility Inspections deficiency.[3] DRM completed a memorandum which deferred the REMS determination until CR deficiencies were addressed.[6]
- **09/22/2021:** The Agency issued a General Advice Letter to the Applicant, including comments for carton and container labeling.[16]
- **11/24/2021:** The Agency received the Class 2 Resubmission.[17]
- **04/11/2022:** DMEPA completed a review that concluded the results of the human factors validation study demonstrated that the representative users could use the product as designed, safely and effectively. The reviewer found the proposed packaging, labels and labeling, and human factors validation study acceptable.[18]
- **05/23/2022**: The Agency issued a CR Letter for facility inspections deficiencies.[4] DRM completed a memorandum which deferred the REMS determination until the deficiencies were addressed.[7]
- **01/23/2023**: The Applicant resubmitted NDA 212905 in response to the CR Letter issued May 23, 2022.[10]
- **02/27/2023**: The Agency issued the Applicant an Acknowledge - Class 2 resubmission letter.[19]

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Molluscum contagiosum is a common, self-limiting, localized infection of the skin in children and adults. It is caused by a double-stranded DNA virus of the poxvirus family, molluscum contagiosum virus. Molluscum contagiosum may occur in all ages, however, it is most common in children. The largest incidence of molluscum contagiosum is in children with a rate of 12-14 episodes per 1000 person

years.[e,20] The reported prevalence in children ranges between 5.1-11.5%.[20] The prevalence in adults has varied over time, however, it is more common in immunocompromised patients and patient with atopic diseases.[21]

Molluscum contagiosum lesions on the skin consist of flesh colored, firm, dome-shaped papules about 2-5 millimeters in diameter. Lesions may occur anywhere on the body, except palms and soles. Infected patients are typically asymptomatic, however, in some cases the lesions may become itchy, sore, and swollen.[21] Molluscum contagiosum is highly transmissible and may be spread by direct skin or mucous membrane transmission or by fomites (e.g. bath towels or sponges). Patients are also at risk of autoinoculation by scratching or rubbing a lesion and spreading it to another location on their body.

Molluscum lesions usually appear 2 to 6 weeks after viral exposure. In immunocompetent patients, the lesions will spontaneously resolve within 6 to 12 months, however, less commonly it can persist for 3 to 6 years. In most patients, there is no scarring or long-term complications after resolution.[f] Because the virus remains only in the epidermis, it cannot be transmitted to others once the lesions are cleared.[21] Although it is benign and self-limiting, it may cause social stigma and stress for infected patients or parents.

3.2 Description of Current Treatment Options

There is no consensus on the need for treatment of molluscum contagiosum in otherwise healthy children and adolescents because the self-limiting nature of the condition.[21-23] Benefits of treatment include prevention of disease transmission and spread, alleviating any discomfort or cosmetic concerns, and prevention of secondary infections. There are currently no FDA approved treatments for the treatment of molluscum contagiosum. Several treatment options include mechanical destruction (e.g., cryotherapy, curettage, pulsed dye laser therapy), topical chemical/drug treatment (e.g., cantharidin, potassium hydroxide, podophyllotoxin, benzoyl peroxide, tretinoin, trichloroacetic acid, lactic acid, glycolic acid, salicylic acid), immune-modulating therapy (e.g., imiquimod, interferon-alpha, cimetidine), and antiviral drug therapy (e.g., cidofovir).[24] Selection of treatment depends on location and extent of the lesions, patient factors (age, comorbid conditions), and patient/caregiver preferences.[25] Treatment risks depend on the selected agent but frequently involve localized skin reactions.

4 Benefit Assessment

The efficacy and safety of cantharidin 0.7% for the treatment of molluscum contagiosum in patients 2 years and older was evaluated in two pivotal phase 3 studies, VP-102-101 (NCT03377790) and VP-102-102 (NCT03377803). The two phase 3 pivotal studies were identical in design: multicenter, randomized,

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[f] 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.*

double-blind, vehicle-controlled, and 12-weeks in duration. Eligible patients were randomized to vehicle or cantharidin (0.7% w/v) topically applied to each molluscum contagiosum lesion for at intervals of 21 days until complete clearance of the lesion or for a maximum of 4 applications. The primary endpoint for both pivotal studies was the proportion of subjects achieving complete clearance of all treatable lesions (baseline and new) at 12 weeks (Day 84).

The studies enrolled 528 subjects 2 years and older with molluscum contagiosum. The results are summarized in Table 1 below. Cantharidin demonstrated statistically significant (p=<0.001) superiority over vehicle for complete clearance of all molluscum contagiosum lesions.

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness for cantharidin for the treatment of molluscum contagiosum. The Agency revised the indication to the following: for the treatment of molluscum contagiosum in adults and pediatric patients 2 years of age and older.[24,g]

Table 1. Percentage of Subjects with Complete Clearance of Molluscum Lesions in Pivotal Studies[26]

	VP-102-101			VP-102-102		
	VP-102 N = 160	**Vehicle N = 106**	**Treatment Difference (95% CI)***	**VP-102 N = 150**	**Vehicle N = 112**	**Treatment Difference (95% CI)***
Day 84	46%	18%	29% (19%, 38%)	54%	13%	40% (30%, 51%)
Day 63	32%	17%	15% (4%, 25%)	28%	5%	23% (15%, 32%)
Day 42	21%	9%	10% (2%, 19%)	13%	4%	9% (3%, 16%)
Day 21	11%	4%	8% (2%, 14%)	5%	2%	3% (-1%, 8%)

CI = confidence interval.

*Treatment difference and 95% CI based on Generalized Estimating Equations (GEE) model for logistic regression with an exchangeable working correlation structure, a factor for treatment, and repeated measurements allowed for a household. Subjects with missing data are imputed as non-responders.

5 Risk Assessment & Safe-Use Conditions

The safety analysis for cantharidin consists of pooled data from randomized subjects who received at least 1 study drug application from the pivotal phase 3 trials, VP-102-101 and VP-102-102, as well as the phase 2 study VP-102-103. The primary safety analysis consisted of pooled data from the two phase 3 trials (N=527). In addition, a safety pool consisting of the two phase 3 trials and the phase 2 study VP-102-103 (N=560) was also reviewed. The majority of patients receiving cantharidin (96%) in the pivotal phase 3 trials experienced at least 1 treatment emergent adverse event compared to 69% receiving

[g] 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.*

vehicle. The most common treatment emergent adverse events were local skin reactions at the application site. The majority of local skin reactions were mild to moderate in severity.

There were no deaths in the clinical development program. In the safety population (Studies VP-102-101, VP-102-102, and VP-102-103), there were no serious adverse reactions[h] reported in any subject who received cantharidin. One subject who received the placebo experienced a serious adverse reaction of acute appendicitis requiring an appendectomy.

The clinical reviewer concluded that the safety data demonstrate that cantharidin appears safe for treatment of molluscum lesions in adults and pediatric patients 2 years of age and older. The reviewer notes that cantharidin has been used for decades safely.[24]

5.1 ACCIDENTAL EXPOSURE

Cantharidin may cause life threatening or fatal toxicities if administered orally. Oral ingestion has resulted in renal failure, blistering and damage to the gastrointestinal tract, coagulopathy, seizures, and flaccid paralysis. Additionally, ocular toxicity (e.g., corneal necrosis, ocular perforation, and deep ocular injuries) can occur if the product comes in contact with eyes.[i]

No cases of accidental exposures occurred in the clinical development program. However, the Agency had concerns about the risk of accidental exposure due to the design of the drug-device interface. In response to the Agency's concerns, the Applicant added a multi-use ampule break tool which was designed to "reduce the force required to break the ampule as well as eliminate the possibility for inadvertent forward spray during the critical break ampule step".[13,27] In addition, several improvements to the user interface were implemented (see section 10.2 for Appendix A for summary of DMEPA recommendations). The proposed cantharidin product has features intended to improve safe use including single use applicator design, addition of a violet-colored dye to assist with identification of where the drug has been applied, and presence of an oral deterrent (denatonium benzoate) to discourage patients from ingesting the drug by biting or licking treated lesions.[12]

Proposed labeling will communicate the risks of cantharidin including the risk of toxicities associated with inappropriate administration in Section 5, Warnings and Precautions. Additionally, labeling will inform healthcare providers to use personal protective equipment including gloves and eye protection. If unintended contact occurs with healthy skin, labeling instructs to remove cantharidin with soap and

[h] 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.

[i] 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.*

water [redacted] (b) (4) Labeling will also include a Patient Package Insert to communicate key risks to patients and caregivers.

The Applicant has proposed to voluntarily provide instruction and training for healthcare providers on the preparation and administration of cantharidin. [redacted] (b) (4) .[28]

6 Expected Postmarket Use

Cantharidin has been used for the treatment of molluscum contagiosum since the 1950s.[9] The likely prescribers and administrators of cantharidin include dermatologists and pediatricians. The safety risks, including the product's flammability and toxicity issues are likely known to these prescribers. They product will be administered by a healthcare provider and will not be self-administered.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a proposed REMS and proposed to utilize labeling and routine post marketing pharmacovigilance surveillance in order to address and identify any potential risks that may be reported for cantharidin. The Applicant has proposed to provide voluntary instruction and training for healthcare providers on the preparation and administration of cantharidin.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of cantharidin on the basis of the efficacy and safety information currently available.

Molluscum contagiosum 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. There are currently no FDA approved treatments for the treatment of molluscum contagiosum, however, several treatment options including topical cantharidin prepared from a bulk substance have been utilized. As cantharidin is currently only available in the United States as a 0.7% concentration in a base of flexible collodion for use in compounding, the Applicant proposes a single-use drug device combination product of topical cantharidin. The product is intended for topical use only and should be administered by a healthcare provider.

The benefit of treatment for the proposed indication for the treatment of molluscum contagiosum was demonstrated in two phase 3 pivotal trials. The indication was revised to "for the topical treatment of molluscum contagiosum in adult and pediatric patients 2 years of age and older".

The risks associated with cantharidin include the toxicities associated with inappropriate administration, local skin reactions, and flammability. The most common adverse events were local skin reactions at the application site. There were no serious adverse events with cantharidin. No cases of accidental exposures occurred in the clinical development program.

Throughout the multiple review cycles, the Agency expressed concerns about the combination drug-device product and the risk of accidental exposure. The Applicant made several changes to address these concerns including addition of a multi-use ampule break tool, improvements to the user interface based on Agency recommendations, and completion of additional human factors validation studies for intended users, including untrained users. DMEPA has found these changes acceptable and do not have additional concerns.[18]

Labeling will communicate the risks of cantharidin including the risk of toxicities associated with inappropriate administration in Section 5, Warnings and Precautions. In addition, labeling will include instructions for use for healthcare providers in Section 2. The instructions for use include the need for healthcare providers to use protective personal equipment (PPE) including gloves and eye protection while preparing and administering cantharidin. Labeling will include instruction to healthcare providers on how to remove cantharidin if unintended contact with healthy skin occurs. Labeling will also include a Patient Package Insert to communicate key risks to patients and caregivers.

The Applicant has proposed voluntary instruction and training for healthcare providers on the preparation and administration of cantharidin. DRM does not object to the proposed voluntary activities; however, as these materials are not part of labeling or a REMS, they should be reviewed by the Office of Prescription Drug Promotion.

Based on the available data, this reviewer concludes a REMS is not necessary to ensure the benefits outweigh the risks associated with cantharidin. Labeling is sufficient to communicate the risks and the instructions for preparation and administration.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The risks of cantharidin are well documented and the likely prescribers should be aware of the risks. Although the proposed single-use drug device combination product is different than the formulations currently available, labeling is sufficient to communicate the risks and appropriate preparation and administration. Labeling negotiations were ongoing at the time of this review.

Should DDD have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

1. Verrica Pharmaceuticals Inc. Original-1 for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. September 13, 2019.
2. Marcus K. Complete Response Letter for cantharidin topical solution, 0.7%, NDA 212905. July 13, 2020.
3. Marcus K. Complete Response Letter for cantharidin topical solution, 0.7%, NDA 212905. September 16, 2021.
4. Marcus K. Complete Response Letter for cantharidin topical solution, 0.7%, NDA 212905. May 23, 2022.
5. Chapman I. Division of Risk Management. REMS Memorandum for Ycanth (cantharidin 0.7% topical solution), NDA 212905. June 15, 2020.
6. Crist L. Division of Risk Management. REMS Memorandum for Ycanth (cantharidin 0.7% topical solution), NDA 212905. September 16, 2021.
7. Crist L. Division of Risk Management. REMS Memorandum for Ycanth (cantharidin 0.7% topical solution), NDA 212905. May 23, 2022.
8. Federal Register. Rules and Regulations. Food and Drug Administration. List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act. Vol. 84, No. 33. Effective March 21, 2019. February 19, 2019.
9. Moed L, Shwayder TA, Chang MW. Cantharidin Revisited: A Blistering Defense of an Ancient Medicine. *Archives of Dermatology.* 2001;137(10):1357-1360.
10. Verrica Pharmaceuticals Inc. Resubmission for Ycanth (cantharidin 0.7%) topical solution, NDA 212905 (Sequence 0069). January 23, 2023.
11. Verrica Pharmaceuticals Inc. Ycanth (cantharidin 0.7%) topical solution. NDA 212905. Module 1.16.1 - Risk Management (Non-REMS). September 13, 2019.
12. Verrica Pharmaceuticals Inc. Safety Update Report for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. January 13, 2023.
13. Verrica Pharmaceuticals Inc. Class 2 Resubmission for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. December 23, 2020.
14. Bhalodia A. Division of Medication Error Prevention and Analysis 1. Human Factors Study Report and Labels and Labeling Review for cantharidin 0.7% topical solution, NDA 212905. September 15, 2021.
15. Schlick J. Division of Medication Error Prevention and Analysis. Label and Labeling and Human Factors Results Review for Ycanth (cantharidin) 0.7% topical solution, NDA 212905. May 27, 2020.
16. Marcus K. General Advice Letter for cantharidin topical solution, 0.7%, NDA 212905. September 22, 2021.
17. Verrica Pharmaceuticals Inc. Resubmission for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. November 24, 2021.
18. Oguntimein M. Division of Medication Error Prevention and Analysis 1. Human Factors Study Report and Labels and Labeling Review for Ycanth (cantharidin) 0.7% topical solution, NDA 212905. April 11, 2022.
19. Song Q. Acknowledge-Class 2 Resubmission Letter for cantharidin topical solution, 0.7%, NDA 212905. February 27, 2023.
20. Olsen JR, Gallacher J, Piguet V, Francis NA. Epidemiology of molluscum contagiosum in children: a systematic review. *Fam Pract.* 2014;31(2):130-136.

21. Center for Disease Conrol and Prevention. Molluscum Contagiosum. Page Updated May 11, 2015. https://www.cdc.gov/poxvirus/molluscum-contagiosum/. Accessed July 23, 2021.
22. Isaacs SN. Molluscum contagiosum. In: MS H, Levy M, Rosen T, Ofori A, eds. *UptoDate*. UptoDate, Waltham, MA. 2020.
23. van der Wouden JC, van der Sande R, Kruithof EJ, Sollie A, van Suijlekom-Smit LW, Koning S. Interventions for cutaneous molluscum contagiosum. *Cochrane Database Syst Rev.* 2017;5(5):Cd004767.
24. Food and Drug Administration. Center for Drug Evaluation and Research. Division of Dermatology and Dentistry. NDA/BLA Multi-Disciplinary Review and Evaluation, Cantharidin NDA 212905. July 9, 2020.
25. Edwards S, Boffa M, Janier M, et al. 2020 European guideline on the management of genital molluscum contagiosum. *Journal of the European Academy of Dermatology and Venereology.* 2021;35(1):17-26.
26. Verrica Pharamceuticals. YCANTH (cantharidin 0.7% topical solution). NDA 212905. DRAFT Prescribing Information. Agency Edits as of June 2023.
27. Verrica Pharmaceuticals Inc. Type A Meeting Request and Package for YCANTH (cantharidin 0.7%) topical solution, NDA 212905 (Sequence 0039). August 31, 2020.
28. Verrica Pharmaceuticals Inc. Human Factors/Response to Information Request for Ycanth (cantharidin 0.7%) topical solution, NDA 212905 (Sequence 0055). May 18, 2021.

10.2 SUMMARY OF PREVIOUS REVIEW CYCLE ASSESSMENT FOR RISK OF ACCIDENTAL EXPOSURE[14,15,18]

Review Cycle	Overview of DMEPA Assessment	Outcome
Review Cycle 1	DMEPA reviewer noted the Human Factors validation study results identified several use errors and use difficulties with critical tasks associated with the use of the combination device. A main concern was the required break force of the ampule and paperboard sleeve could lead to accidental exposure to the user's mouth or eye. The reviewer concluded that additional mitigation strategies were necessary such as device design changes to optimize the applicator and other revisions to the product user interface (e.g., readability of the Instructions for Use).	Complete response letter included a human factors deficiency
Review Cycle 2	The Applicant proposed adding a break tool to assist with reducing the force needed to break the ampule and made changes to the user interface and carton and container labeling. In addition, the Applicant informed the Agency that they intended to deploy a training	General Advice Letter issued to Applicant which included recommendations for improving the proposed user interface and carton and container labeling to ensure safe use of the product.

	program to train real-world users prior to product use. (b) (4) The DMEPA reviewer expressed concerns that it was unclear how the Applicant would ensure all users would receive training and recommended a supplemental HF validation study with untrained users. The results of the human factors validation study identified use errors with critical tasks, even in trained users. The reviewer remained concerned about residual risk associated with accidental exposure to skin or eyes.	Another human factors validation study was recommended to evaluate changes implemented. The reviewer recommended the study include untrained healthcare professionals as a distinct user group.
Review Cycle 3	A supplemental human factors validation study was completed in December 2021 which included 16 untrained healthcare providers to evaluate the implemented changes to the user interface. Of note, the Applicant voluntarily proposes to provide instruction and training to all healthcare providers on the preparation and administration of cantharidin; however, this study included untrained providers and represents a "worst case" scenario. One use error was identified and included a participant who did not inspect the applicator according to the instructions for use due to failure to remove the paperboard sleeve. The Applicant noted this study reflected a decrease in use errors compared to an earlier human factors study in May 2021. The Applicant concluded the implemented changes are effective. The DMEPA reviewer concluded the results of the human factors study demonstrated that representative users could use the product, as designed, safely and effectively. They did not have further recommendations or concerns about the proposed package, label and labeling.	DMEPA found the proposed packaging, labels and labeling, and HF factors validation study acceptable. No additional recommendations.

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07/20/2023 11:06:30 AM

CYNTHIA L LACIVITA
07/20/2023 11:06:48 AM

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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	212905
PDUFA Goal Date	May 24, 2022
OSE RCM #	2019-1921
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	May 23, 2022
Subject	Defer comment on evaluation of need for a REMS
Established Name	Cantharidin 0.7% solution for topical administration
Trade Name	Ycanth
Name of Applicant	Verrica Pharmaceuticals, Inc
Therapeutic Class	Vesicant
Formulation(s)	Topical solution
Dosing Regimen	No more than two applicators for one treatment session; apply sufficient amount to cover the area. Cantharidin may be administered to treatable lesions every 3 weeks until all lesions are cleared.

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1 Introduction

This memorandum (memo) documents the deferral of a Risk Evaluation and Mitigation Strategy (REMS) review for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. Verrica Pharmaceuticals, Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 212905 on September 13, 2019 under the 505(b)(1) regulatory pathway for the treatment of molluscum contagiosum.[1] This drug product is not a new molecular entity (NME). The safety concerns associated with cantharidin include the risks of inappropriate administration, local skin reactions, and flammability.

A Complete Response Letter was issued to the Applicant on July 13, 2020 outlining deficiencies with Product Quality, Facilities, Process (manufacturing), and Human Factors.[2] The Division of Risk Management (DRM) completed a memo on June 15, 2020 which deferred the REMS determination until the deficiencies were addressed.[3] The Agency issued a second CR Letter on September 16, 2021 based on a Facility Inspections deficiency.[4] DRM completed a memorandum which deferred the REMS determination until the deficiencies were addressed.[5] The Agency issued a General Advice letter to communicate recommendations for carton and container labeling to improve the proposed user interface in order to ensure safe and effective use of the product on September 22, 2021.[6]

The Applicant submitted a Class 2 resubmission in response to the Complete Response on November 24, 2021.[7] The Applicant did not submit a proposed REMS and proposed to utilize labeling (Prescribing Information, Instructions for Use (for healthcare providers), and a Patient Information Leaflet and continuous routine post marketing pharmacovigilance surveillance in order to address and identify any potential risks that may be reported for cantharidin.[8] This application is under review in the Division of Dermatology and Dentistry (DDD).

2 Background

2.1 Product Information

Ycanth (cantharidin 0.7%) topical solution is proposed for the treatment of molluscum contagiosum. The active ingredient, cantharidin, is a naturally occurring lipophilic compound from the body fluids of the blister beetle that functions as a vesicant when topically applied to the skin. Topical cantharidin has been used by healthcare providers for the treatment of dermatologic conditions, including warts and molluscum contagiosum since the 1950s; however, it is not FDA approved for any indication in the United States.[9] It is currently available in the United States as a 0.7% concentration in a base of flexible collodion for use in compounding, and it is included on the "List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act," a rule by the Food and Drug Administration.[10]

The Applicant proposed a single-use drug device combination product containing cantharidin 0.7% (b) (4) solution for topical administration.[1,7,11] The to-be-marked product is proposed to be supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a

protective paperboard sleeve. Each ampule of cantharidin contains 0.45 mL of 0.7% (w/v) cantharidin solution.

Cantharidin is intended to be administered only by a healthcare professional. The proposed dosage is as follows: administer to each treatable lesion a single application of the volume of cantharidin needed to cover each lesion, taking care to avoid adjacent healthy skin. Cantharidin should remain on lesions for 24 hours for optimal effectiveness. In the event that cantharidin causes significant blistering, significant pain or other adverse events, cantharidin may be removed by washing with soap and water prior to 24 hours. Cantharidin may be administered to treatable lesions every 3 weeks until all lesions are cleared.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212905 relevant to this review:

- **09/13/2019:** A 505(b)(1) application (NDA 212905) submission was received for Ycanth (cantharidin 0.7%) topical solution.[1]
- **06/15/2020:** DRM completed a memorandum which deferred the REMS determination until CR deficiencies were addressed.[3]
- **07/13/2020:** The Agency issued a Complete Response for Product Quality, Facilities, Process (manufacturing), and Human Factors deficiencies.[2]
- **12/23/2020:** The Agency received the Class 2 Resubmission[11]
- **09/16/2021**: The Agency issued a CR Letter for a Facility Inspections deficiency.[4] DRM completed a memorandum which deferred the REMS determination until CR deficiencies were addressed.[5]
- **09/22/2021:** The Agency issued a General Advice Letter to the Applicant, including comments for carton and container labeling.[6]
- **11/24/2021:** The Agency received the Class 2 Resubmission.[7]

3 Conclusion & Recommendations

DDD plans to issue a Complete Response letter citing Facilities deficiencies. Review of final labeling was deferred at this time. Therefore, DRM defers comment on the need for a REMS at this time. An evaluation of the need for a REMS for Ycanth (cantharidin 0.7%) topical solution will be completed after the Applicant addresses the identified deficiencies. This memo serves to close the existing assignment for cantharidin 0.7% topical solution under NDA 212905.

Please notify DRM if there are any questions.

4 References

1. Verrica Pharmaceuticals Inc. Original-1 for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. September 13, 2019.

2. Marcus K. Complete Response Letter for cantharidin topical solution, 0.7%, NDA 212905. July 13, 2020.
3. Chapman I. Division of Risk Management. REMS Memorandum for Ycanth (cantharidin 0.7% topical solution), NDA 212905. June 15, 2020.
4. Marcus K. Complete Response Letter for cantharidin topical solution, 0.7%, NDA 212905. September 16, 2021.
5. Crist L. Division of Risk Management. REMS Memorandum for Ycanth (cantharidin 0.7% topical solution), NDA 212905. September 16, 2021.
6. Marcus K. General Advice Letter for cantharidin topical solution, 0.7%, NDA 212905. September 22, 2021.
7. Verrica Pharmaceuticals Inc. Resubmission for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. November 24, 2021.
8. Verrica Pharmaceuticals Inc. Ycanth (cantharidin 0.7%) topical solution. NDA 212905. Module 1.16.1 - Risk Management (Non-REMS). September 13, 2019.
9. Moed L, Shwayder TA, Chang MW. Cantharidin Revisited: A Blistering Defense of an Ancient Medicine. *Archives of Dermatology.* 2001;137(10):1357-1360.
10. Federal Register. Rules and Regulations. Food and Drug Administration. List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act. Vol. 84, No. 33. Effective March 21, 2019. February 19, 2019.
11. Verrica Pharmaceuticals Inc. Class 2 Resubmission for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. December 23, 2020.

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LINDSEY W CRIST
05/23/2022 10:25:58 AM

CYNTHIA L LACIVITA
05/23/2022 10:44:55 AM

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	212905
PDUFA Goal Date	September 23, 2021
OSE RCM #	2019-1921
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS Ingrid N. Chapman, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	September 16, 2021
Subject	Defer comment on evaluation of need for a REMS
Established Name	Cantharidin 0.7% solution for topical administration
Trade Name	Ycanth
Name of Applicant	Verrica Pharmaceuticals, Inc
Therapeutic Class	Vesicant
Formulation(s)	Topical solution
Dosing Regimen	No more than two applicators for one treatment session; apply sufficient amount to cover the area. Cantharidin may be administered to treatable lesions every 3 weeks until all lesions are cleared.

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1 Introduction

This memorandum (memo) documents the deferral of a Risk Evaluation and Mitigation Strategy (REMS) review for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. Verrica Pharmaceuticals, Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 212905 on September 13, 2019 under the 505(b)(1) regulatory pathway for the treatment of molluscum contagiosum.[1] This drug product is not a new molecular entity (NME). [a] The risks associated with cantharidin include the toxicities associated with inappropriate administration, local skin reactions, and flammability. A Complete Response Letter was issued to the Applicant on July 13, 2020 outlining deficiencies with Product Quality, Facilities, Process (manufacturing), and Human Factors.[2] The Division of Risk Management (DRM) completed a memo on June 15, 2020 which deferred the REMS determination until the deficiencies were addressed.[3]

The Applicant submitted a Class 2 resubmission in response to the Complete Response on December 23, 2020.[4] The Applicant did not submit a proposed REMS and proposed to utilize labeling (Prescribing Information, Instructions for Use (for healthcare providers), and a Patient Information Leaflet and continuous routine post marketing pharmacovigilance surveillance in order to address and identify any potential risks that may be reported for cantharidin.[5] This application is under review in the Division of Dermatology and Dentistry (DDD).

2 Background

2.1 Product Information

Ycanth (cantharidin 0.7%) topical solution is proposed for the treatment of molluscum contagiosum. The active ingredient, cantharidin, is a naturally occurring lipophilic compound from the body fluids of the blister beetle that functions as a vesicant when topically applied to the skin. Topical cantharidin has been used by healthcare providers for the treatment of dermatologic conditions, including warts and molluscum contagiosum since the 1950s; however, it is not FDA approved for any indication in the United States.[6] It is currently available in the United States as a 0.7% concentration in a base of flexible collodion for use in compounding, and it is included on the "List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act," a rule by the Food and Drug Administration.[7]

The Applicant proposed a single-use drug device combination product containing cantharidin 0.7% (b) (4) solution for topical administration.[4] The to-be-marked product is proposed to be supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. Each ampule of cantharidin contains 0.45 mL of 0.7% (b) (4) cantharidin solution.

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

Cantharidin is intended to be administered only by a healthcare professional. The proposed dosage is as follows: administer to each treatable lesion a single application of the volume of cantharidin needed to cover each lesion, taking care to avoid adjacent healthy skin. Cantharidin should remain on lesions for 24 hours for optimal effectiveness. In the event that cantharidin causes significant blistering, significant pain or other adverse events, cantharidin may be removed by washing with soap and water prior to 24 hours. Cantharidin may be administered to treatable lesions every 3 weeks until all lesions are cleared.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212905 relevant to this review:

- 09/13/2019: A 505(b)(1) application (NDA 212905) submission was received for Ycanth (cantharidin 0.7%) topical solution.[1]
- 07/13/2020: The Agency issued a Complete Response for Product Quality, Facilities, Process (manufacturing), and Human Factors deficiencies.[2]
- 12/23/2020: Class 2 Resubmission[4]
- 05/04/2021: The FDA issued a Discipline Review Letter to the Applicant for deficiencies with the study methodology of the human factors validation study.
- 05/26/2021: The Agency issued a Major Amendment Acknowledgement Letter to the Applicant extending the PDUFA goal date 3 months.
- 06/18/2021: The Applicant submitted the human factors study report in response to the Discipline Review Letter issued on 05/04/2021.

3 Conclusion & Recommendations

DDD plans to issue a Complete Response letter based on Chemistry, Manufacturing, and Control (CMC) related deficiencies, specifically Facilities deficiencies. Review of final labeling was deferred at this time. Therefore, DRM defers comment on the need for a REMS at this time. An evaluation of the need for a REMS for Ycanth (cantharidin 0.7%) topical solution will be completed after the Applicant addresses the identified deficiencies. This memo serves to close the existing consult request to DRM for cantharidin 0.7% topical solution under NDA 212905.

Please notify DRM if there are any questions.

4 References

1. Verrica Pharmaceuticals Inc. Original-1 for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. September 13, 2019.
2. Marcus K. Complete Response Letter for cantharidin topical solution, 0.7%, NDA 212905. July 13, 2020.

3. Chapman I. Division of Risk Management. REMS Memorandum for Ycanth (cantharidin 0.7% topical solution), NDA 212905. June 15, 2020.
4. Verrica Pharmaceuticals Inc. Class 2 Resubmission for Ycanth (cantharidin 0.7%) topical solution, NDA 212905. December 23, 2020.
5. Verrica Pharmaceuticals Inc. Ycanth (cantharidin 0.7%) topical solution. NDA 212905. Module 1.16.1 - Risk Management (Non-REMS). September 13, 2019.
6. Moed L, Shwayder TA, Chang MW. Cantharidin Revisited: A Blistering Defense of an Ancient Medicine. *Archives of Dermatology.* 2001;137(10):1357-1360.
7. Federal Register. Rules and Regulations. Food and Drug Administration. List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act. Vol. 84, No. 33. Effective March 21, 2019. February 19, 2019.

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LINDSEY W CRIST
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JACQUELINE E SHEPPARD
09/16/2021 01:04:14 PM

DORIS A AUTH
09/16/2021 01:17:33 PM

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	212905
PDUFA Goal Date	July 20, 2020
OSE RCM #	2019-1921
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Acting Team Leader	Jacqueline Sheppard, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 15, 2020
Subject	Defer comment on DRM evaluation of the need for a REMS
Established Name	Cantharidin 0.07% solution for topical administration
Trade Name	Ycanth
Name of Applicant	Verrica Pharmaceuticals, Inc
Therapeutic Class	Vesicant
Formulation(s)	Topical solution
Dosing Regimen	No more than two applicators for one treatment session; apply sufficient amount to cover the area. Cantharidin may be administered to treatable lesions every 3 weeks until all lesions are cleared.

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1 Introduction

This memo is to defer the Division of Risk Management's (DRM) review of the need for a risk evaluation and mitigation strategy (REMS) for Ycanth (cantharidin 0.07%) topical solution, NDA 212905.

Verrica Pharmaceuticals, Inc submitted a 505(b)(1) application for Ycanth (cantharidin 0.07%) topical solution on September 13, 2019 for the proposed indication: treatment of molluscum contagiosum. This drug product is not a new molecular entity (NME).[a] The risks associated with cantharidin include severe local skin reactions (application site), systemic toxicity, and flammability. The Applicant did not submit a proposed REMS and proposed to utilize continuous routine post marketing pharmacovigilance surveillance in order to address and identify any potential risks that may be reported for cantharidin.[1] This application is under review in the Division of Dermatology and Dentistry (DDD).

2 Product Information

2.1 PRODUCT INFORMATION[2]

Ycanth (cantharidin 0.07%) topical solution is a (b) (4) proposed for the treatment of molluscum contagiosum. Cantharidin, proposed as a 0.7% (b) (4) solution for topical administration, is supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. Each ampule of cantharidin contains 0.45 mL of 0.7% (b) (4) cantharidin solution. The recommended dose is as follows: administer to each treatable lesion a single application of the volume of cantharidin needed to cover each lesion, taking care to avoid adjacent healthy skin. Cantharidin should remain on lesions for 24 hours for optimal effectiveness. In the event that cantharidin causes significant blistering, significant pain or other adverse events, cantharidin may be removed by washing with soap and water prior to 24 hours. Cantharidin may be administered to treatable lesions every 3 weeks until all lesions are cleared.[b]

Cantharidin is not currently FDA-approved for use in the United States. However, in 2019, cantharidin was included in the, "List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act," a rule by the Food and Drug Administration.[3]

Cantharidin is marketed by Health Canada as the following two products:

1. Drug Product (market date 12/31/1984)[4]
    a. Brand name: Cantharone Plus (cantharidin 1%, podophyllin 2%, and salicylic acid 30%; 7.5 mL bulk bottle)

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

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

b. Indications and Usage: for removal of warts, especially plantar and resistant and heavily keratinized warts. Painless application and the absence of instruments makes it a simple wart treatment procedure. Some pain may occur later.

2. Natural Product (date of licensing: 02/25/2011)[5]
   a. Brand name: Cantharone Liquid (cantharidin 0.7%; 7.5 mL bulk bottle)
   b. Recommended use or purpose: Cantharone is indicated for removal of warts and Molluscum contagiosum. Painless application and the absence of instruments make it a simple wart treatment procedure. Some pain may occur later.

The products approved by Health Canada both have the following warning:[6]

> Cantharone and Cantharone Plus are for physician use only. They should not be dispensed or prescribed for patient administration under any circumstances.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212905 relevant to this review:

- 09/13/2019: A 505(b)(1) application (NDA 212905) submission was received for Ycanth (cantharidin 0.07%) topical solution.
- 02/26/2020: The FDA issued a Discipline Review Letter to the Applicant to convey the deficiencies identified during review of NDA 212905 in the Human Factors study, drug product stability, and facility registration.
- 03/04/2020: The Applicant submitted a response to the Discipline Review Letter issued on 02/26/2020.
- 03/23/2020: The FDA issued a Discipline Review Letter to the Applicant in response to the submission received on 03/04/2020 regarding drug product stability issues and the Human Factors study.

3 Substantial Review Issues

3.1 DEVICE AND COMPANION DIAGNOSTIC ISSUES[7]

The Division of Medication Error Prevention and Analysis (DMEPA) expressed concerns that the proposed cantharidin combination product is not safe and effective for use by health care providers (HCPs), stating that the risk for accidental exposure outweighs the benefit of the treatment with this combination product. The inherent design of this product may contribute to serious harm if accidental exposure occurs during use. In particular, the break force of the ampule and paperboard sleeve have been points of concern as identified through use-related risk analysis (URRA), Human Factors study design, and observed errors/close calls/use difficulties with critical and non-critical tasks. Mitigation strategies are needed and could include the need for device design changes to optimize the applicator, as well as other revisions to the product user interface (e.g., readability of the Instructions for Use).

3.2 PRODUCT QUALITY

The drug product reviewer from the Office of Pharmaceutical Quality (OPQ) recommended that this NDA cannot be approved due to the following deficiencies:[8]

1. The proposed drug product specification does not include tests to assure the drug product can be safely and accurately expelled onto the lesion area and avoid the adjacent healthy skin.
2. The extraction solutions, [redacted] (b) (4) used in the extractable/leachable study are considered inadequate.
3. The drug product quality is not assured and the expiration dating period cannot be established because the registration drug product batches provided in the application were not fully assembled [redacted] (b) (4)

4 Conclusion & Recommendations

The review division recommends a complete response on the basis that the demonstrated benefit was insufficient to outweigh the identified safety concerns. Because benefit-risk has not been determined, DRM is currently unable to formulate recommendations for risk management, specifically the need for a REMS. An evaluation of the need for a REMS for Ycanth (cantharidin 0.07%) topical solution will be completed after the Applicant addresses the identified deficiencies. This memo serves to close the existing consult request to DRM for cantharidin 0.07% topical solution under NDA 212905.

5 Appendices

5.1 REFERENCES

1. Verrica Pharmaceuticals Inc. Ycanth (cantharidin 0.7%) topical solution. NDA 212905. Module 1.16.1 - Risk Management (Non-REMS). September 13, 2019.
2. Verrica Pharmaceuticals Inc. Ycanth (cantharidin 0.7%) topical solution. NDA 212905. Prescribing Information, draft. September 13, 2019.
3. Federal Register. Rules and Regulations. Food and Drug Administration. List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act. Vol. 84, No. 33. Effective March 21, 2019. February 19, 2019.
4. Health Canada - Drug Product Database. Product Information - Cantharone Plus. March 19, 2019.
5. Health Canada. Licensed Natural Helath Products Database. Product Information - Cantharone Liquid 0.7%. February 6, 2018.
6. Dormer Laboratories, Inc. Cantharone and Cantharone Plus. http://www.dormer.com/Cantharone/AccDetail.aspx?ID=9001-975M. Accessed May 22, 2020.
7. Food and Drug Administration. Division of Dermatology and Dentistry. Ycanth (cantharidin). NDA 212905. Unireview, draft. June 8, 2020.
8. Food and Drug Administration. Office of Pharmaceutical Quality. Integrated Quality Review. June 11, 2020.

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/s/

INGRID N CHAPMAN
06/15/2020 09:12:56 AM

JACQUELINE E SHEPPARD
06/15/2020 02:37:40 PM

CYNTHIA L LACIVITA
06/16/2020 04:49:04 PM