Summary Report

Cantharidin

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

January 2020

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

Table of Tables

REVIEW OF NOMINATIONS

Cantharidin (UNII code: IGL471WQ8P) was nominated for inclusion on the 503B Bulks List by the the Specialty Sterile Pharmaceutical Society (SSPS) and the Outsourcing Facilities Association (OFA). While the exact medical condition in which the compounded product is being request may be unknown, cantharidin is generally used to treat warts. Cantharidin will be compounded as a 0.7-1% nonsterile topical solution, or based on the prescriber's request. Cantharidin was nominated for use in combination with podophyllum resin and salicylic acid, refer to Table 7 for the nominated combination formulations.

Reasons provided for nomination to the 503B Bulks List include:

- Prescribers and hospital formularies have different preferences or requirements for concentrations, volumes, or final product containers for administration.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is more safe and efficient.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state-of-the-art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.
- There are no FDA-approved drugs containing this active pharmaceutical ingredient (API).
- Patients respond differently to drug products and the compounded products may be the only formulations that can effectively treat the intended indication.
- Compounding from bulk allows using only the necessary ingredients to achieve the desired clinical outcome. The API will be without any fillers, excipients, fillers, binders, dyes, preservatives, or other materials ensuring that no irritating, hazardous, or allergen ingredients are included.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of cantharidin products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA) and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for cantharidin; name variations of cantharidin were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or

schedule; approval date. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing cantharidin. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

Two databases (PubMed and Embase) were searched including any date through January 23, 2019. The search included a combination of (cantharidin[TIAB] OR cantharidin [TIAB] OR cantharides[TIAB]) AND (treatment[TIAB] OR therapy[TIAB] OR therapeutic*[TIAB] OR clinical[TIAB] OR wart*[TIAB] OR topical[TIAB] OR skin[TIAB] OR derm*[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of cantharidin or the implementation of cantharidin in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

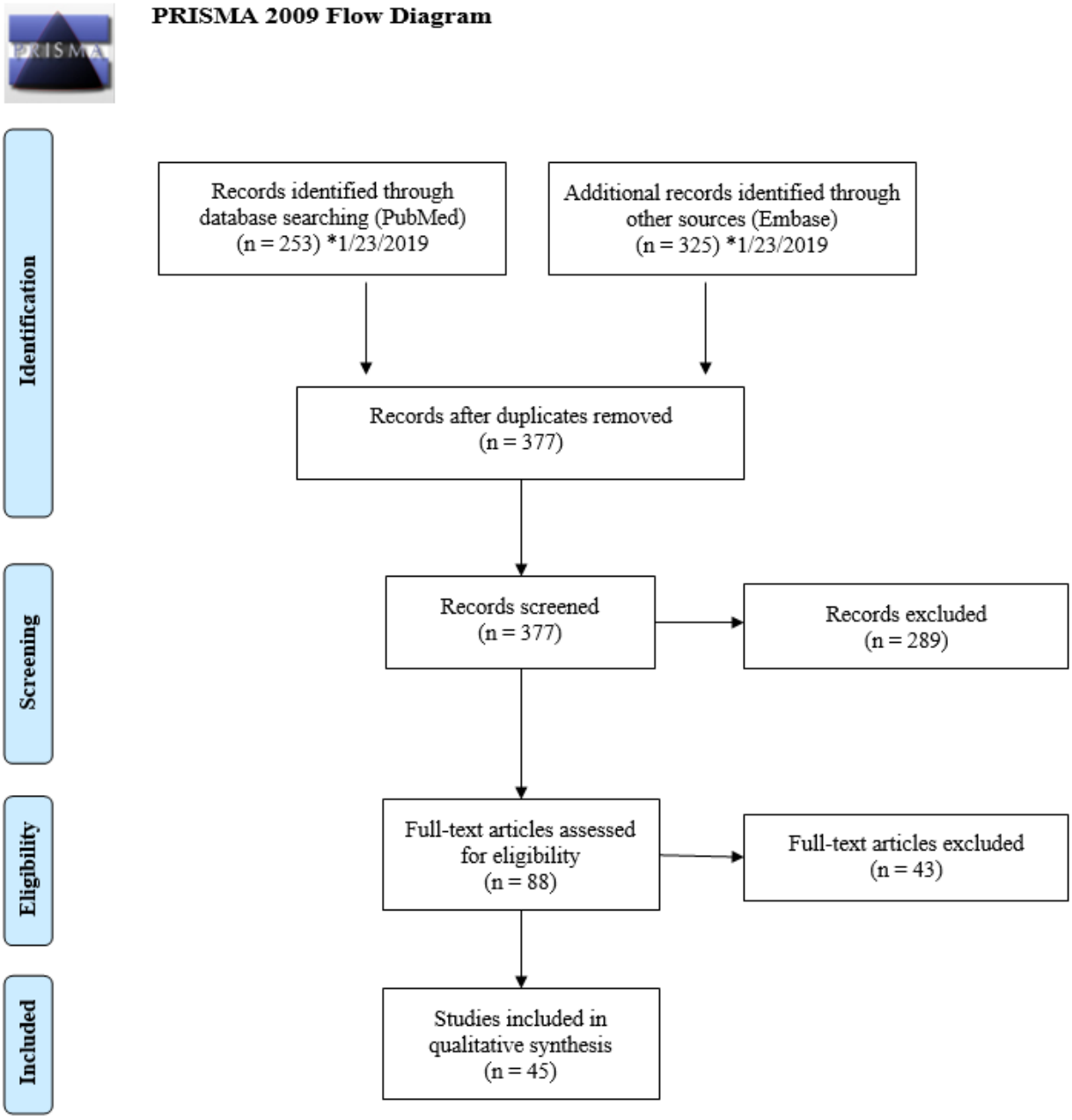
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for cantharidin use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of cantharidin compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indication from the nomination and the results of the literature review, two (2) medical specialties that would potentially use cantharidin were identified: dermatology and oncology. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. One (1) expert was contacted for interviews, of which one (1) accepted. The second medical expert failed to respond to the interview request. The interview was recorded and transcribed via ©Rev.com. QSR International's Nvivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for dermatology and oncology, identified from the nomination, literature review, and interview, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to five (5) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Oncology	American Society of Clinical Oncology (ASCO)	Declined, "they are unable to share survey with members"

CURRENT AND HISTORIC USE

Summary of background information

- Cantharidin is not available as an FDA-approved product.
- Cantharidin is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for cantharidin.
- Cantharidin is available in Canada.

Table 3. Currently approved products – US

No approved products in the US

Table 4. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
Cantharidin, podophyllin, salicylic acid	1%, 2%, 30%	Liquid	Topical	Canada	Prescription	12/31/1984

Abbreviations: "–", not mentioned; ROA, route of administration.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Summary of literature review

- Cantharidin has been used for many centuries. For dermatology, it has been used for molluscum contagiosum and warts since the 1950s. In 1962, the FDA required all food, drug, and cosmetic manufacturers to provide efficacy data for their products, but the manufacturers for cantharidin failed to provide the required data, as a result it was removed from the market. In 1997, cantharidin was reintroduced on the FDA bulk substance list which allowed cantharidin to be topically applied by a physician in a professional setting.[1]
- Total number of studies included: 45 studies (28 descriptive, 13 experimental, and 4 observational).
- Most of the studies were from the US (29).
- There were four (4) studies identified with the nominated combination.
- The most common indications for the use of cantharidin in both the US and non-US studies were molluscum contagiosum and warts.
- Nine (9) US studies were identified that used cantharadin as a 0.7% compounded solution for warts and molluscum contagiosum.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1–28]	28
Experimental[29–41]	13
Observational[42–45]	4

Table 6. Number of studies by country

Country	Number of Studies
Australia[16]	1
Canada[37]	1
China[3,20,21]	3
Egypt[34]	1
Germany[17]	1
Iran[41]	1
Israel[22]	1
Spain[15,40,42]	3
Turkey[38,39]	2

UK[33]	1
US[1,2,4–14,18,23–32,35,36,43–45]	29
Multiple Countries • Australia, US[19]	1
	Total US[a]: 30 Total non-US Countries[a]: 16

[a]Study 19 counted in both US and non-US total

Table 7. Number of studies by combinations

	Combination Formula	**Number of Studies**
Nominated	Cantharidin 1% / Podophyllum resin 5% / Salicylic acid 30%[13,29,32,33]	4
Others found in literature	Cantharidin 0.7% / Salicylic acid plaster 40%[11]	1
	Cantharidin 1% / Podophyllum resin 20% / Salicylic acid 30%[34]	1
	Cantharidin 1% / Podophyllotoxin 5% / Salicylic acid 30%[5,38,40,42]	4

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Molluscum contagiosum[1,2,4,7,9,12,23,24,27,28,30,35,36,45]	–	0.7-0.9%	Solution	Once	Once-Every 1-8 weeks as needed
Warts[5,8,11–14,18,25,26,31,32,43,44]	–	0.7-3%	Solution	Topical	Once-Every 1-4 weeks as needed
Acquired perforating dermatosis[19]	–	1%	–	Topical	Once
Callus removal[29]	–	1%	Solution	Topical	Once
Intractable plantar lesion[10]	–	–	Solution	Topical	Once
Porokeratosis of Mibelli[6]	–	0.7%	Solution	Topical	Once

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Warts[33,34,38–42]	–	0.07-1%	Solution	Topical	Once-30 months
Molluscum contagiosum[15,16,37]	0.2 mL/a lesion	0.2-0.7%	Solution	Topical	Once-Thrice
Non-small cell lung cancer[20,21]	40-100mL/day	–	Injection	Intravenous	7-28 days for 1-4 cycles
Acquired perforating dermatosis[19]	–	1%	–	Topical	Once
Colorectal cancer[3]	–	–	Injection	–	–
Herpes zoster[17]	–	–	Patch	Topical	2 weeks
Ocular leprosy[22]	–	–	Autoserum	Ophthalmic	–

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Molluscum contagiosum[2,27,28,30,35,36,45]	1961-2018	• "Compounded by a local pharmacist for use in clinic"[2]	–	–
		• Single-use vial produced under good manufacturing practices[35]	Solution	0.7%
		• Cantharidin crystals in acetone, hydroxypropylcellulose, and flexible collodion[30,36]		0.7%
		• Cantharidin in equal parts acetone and flexible collodion[27,28]		0.9%
		• Cantharidin crystals in flexible collodion[45]		0.7%
Warts[11,26]	1961, 1958	• Cantharidin in equal parts acetone and flexible collodion	Solution	0.7%

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

No compounded products from reported studies

Summary of focus groups/interviews of medical experts and specialty organizations

One (1) interview was conducted.

Table 12. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Cantharidin	Interview Summary Response
DER_04	MD	Dermatology Dermatology/Immunology	Independent Consultant	Yes	• There is a need for office stock. • If cantharidin was patient specific, there are some safety concerns with parents/guardians over applying or forgetting to wash the cantharidin off. • Lots of historical use. • Cantharidin is not first line but has supplemental treatment value.

Abbreviation: MD, Doctor of Medicine.

Background:

- Per the interviewee, there was a lot of historical use when it was available to dermatologists until the FDA decided to clean up some of these old products that would not meet the current standards for demonstrating safety and efficacy leading to it being taken off the market.

Indications:

- Warts or molluscum

Previous experience with cantharidin

- Interviewee used it as a solution, does not recall the strength
- Historically, providers would obtain cantharadin as a non-patient specific 10mL bottle from the university pharmacy.
- Patients would receive treatment on one area once every two weeks.
- The interviewee stated that cantharadin was frequently used stating that a pediatric dermatologist might see two or three patients a day with molluscum.

Need for office stock

- The interviewee stated that after cantharidin was taken off the market, many dermatologists were getting it from Canada and using it in their offices.
- The interviewee highly recommended keeping this available as office stock because it is used by a large number of dermatologists who know how to use safely use it. Cantharidin has been available for a really long time, "probably like over a hundred years."
- The interviewee had safety concerns regarding allowing parents or guardians to obtain cantharidin for at-home application due to over-applying or forgetting to wash the cantharidin off, which could cause blisters that develop into erosions or ulcers.

Cantharidin compared to other alternatives:

- The interviewee stated that cantharidin is useful in treating children in the office because it does not hurt upon application and "…later when they go home that they start to blister, but they don't remember that it happened because of what you did to them in the office."
    - There has not been anything to replace cantharidin until now. A company (Verica) has just completed studies on a product for treating molluscum contagiosum.
    - The interviewee stated that cantharidin has somewhat marginal efficacy but can be used as a supplement. For example, "[the patient] got pretreated with imiquimod and [the patient] came in and…still had some areas that were involved."
    - For warts and molluscum, the interviewee did not think cantharidin is "necessarily first line," but is nice to have as part of the treatment approach.
- Liquid nitrogen or cryotherapy are alternatives, however the problem with using treatments is that it hurts upon application and could be traumatizing to children.
- Imiquimod is only indicated for warts, not molluscum because there was a study that showed lack of efficacy in use. Imiquimod is also user friendly because patients are able to use it at home.

Summary of survey results

Table 13. Characteristics of survey respondents [5 people responded to the survey]

Board Certification	MD	No Response
Dermatology	2	0
No Board Certification	0	0
No Response	0	3

Abbreviation: MD, Doctor of Medicine

Table 14. Types of products used, prescribed, or recommended

Types of Products	Respondents, n (N=3[a])
Compounded	3[b]
FDA-approved	1
Over-the-counter	0
Dietary	0
Unsure	0
No response	0

[a]Out of five (5) respondents, three (3) reported using, prescribing, or recommending multiple types of cantharidin product.
[b]One (1) respondent used in combination: Cantharidin/salicylic acid.

Table 15. Compounded use of cantharidin in practice[a]

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Molluscum contagiosum	0.7%	Every 2 weeks	Liquid	Topical	Until resolved	Pediatric
	–	–	Colloid, solution		–	–
Verruca plana	0.7%	Every 2 weeks	Liquid	Topical	Until resolved	Pediatric, adult
Warts	–	–	–	–	–	–

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Two (2) respondents.

Table 16. Indications for which cantharidin is considered standard therapy

Indication	Standard Therapy	
	Compounded, n (N=3[a])	Non-compounded, n (N=1)
Molluscum contagiosum	2	0
Warts	1	0
No response	1	0

[a]Some respondents reported more than one indication.

Table 17. Reasons for using a compounded product instead of any FDA-approved product

Reasons
"Painless. High degree of efficacy. Reduced risk of scarring. Applied in office / controlled setting."
"No FDA approved treatment"

Table 18. Change in frequency of compounded cantharidin usage over the past 5 years

	Respondents, n (N=3)
No–use has remained consistent	0
Yes–I use it LESS often now[a]	1
Yes–I use it MORE often now[b]	1
No response	1

[a]One (1) respondent wrote "compounding shortage."
[b]One (1) respondent wrote "more pediatric patients."

Table 19. Do you stock non-patient specific compounded cantharidin in your practice?

	Respondents, n (N=4)
No	0
Yes	2
No Response	1

Table 20. Questions related to stocking non-patient specific compounded cantharidin

	Respondents, n (N=3)
In what practice location(s) do you stock non-patient-specific compounded cantharidin? (n=3[a])	
Physician office	2
Outpatient clinic	1
Emergency room	0
Operating room	0
Inpatient ward	0
Other	0
No response	1
How do you obtain your stock of non-patient-specific compounded cantharidin? (n=3)	
Purchase from a compounding pharmacy	0
Purchase from an outsourcing facility	0
Compound the product yourself	0
Other	0
No response	3
Why do you keep a stock of non-patient-specific compounded cantharidin? (n=3)	
Convenience	2
Emergencies	0
Other	0
No response	1

[a]One (1) respondent reported stocking non-patient-specific compounded cantharidin in more than one location.

CONCLUSION

Cantharidin (UNII code: IGL471WQ8P) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society (SSPS) and the Outsourcing Facilities Association (OFA). While the exact medical condition in which the compounded product is being request may be unknown, cantharidin is generally used to treat warts. Cantharidin will be compounded as a 0.7-1% nonsterile topical solution, or based on the prescriber's request. Cantharidin was nominated for use in combination with podophyllum resin and salicylic acid, refer to Table 7 for the nominated combination formulations. Cantharidin is not available as an FDA-approved or an OTC product. There is there a current USP monograph. Cantharidin is available in Canada.

From the literature review, the most common indications for the use of cantharidin in both the US and non-US studies were molluscum contagiosum and warts. Nine (9) US studies identified the use of cantharidin as a 0.7% compounded solution for treatment of warts and mulloscum contagiosum. There were four (4) studies identified that utilized cantharidin in one of the nominated combination.

From the interview, the interviewee stated that cantharidin is a drug with lots of historical use. Although the interviewee did not consider cantharidin first line, it does have value as a supplemental treatment. If cantharidin was provided as patient-specific prescriptions and administered at home, there are safety concerns with parents or guardians over-applying or forgetting to wash the cantharidin off.

From the survey responses, three (3) out of five (5) respondents used cantharidin. Three (3) respondents used compounded cantharidin and one (1) respondent reported using cantharidin in combination with salicylic acid. Two (2) respondents stated they use compounded cantharidin for molluscum contagiosum, verruca plana, and warts. The reasons for using the compounded product are because there is no FDA-approved treatment, it is painless with a high degree of efficacy, it reduces the risk of scarring, and it is applied in the office/controlled setting. Two (2) respondents stock non-patient specific compounding cantharidin in a physician office and outpatient clinic. They reported obtaining cantharidin through a compounding pharmacy and maintain an office stock convenience.

APPENDICES

Appendix 1. References

1. Cathcart S, Coloe J, Morrell DS. Parental satisfaction, efficacy, and adverse events in 54 patients treated with cantharidin for molluscum contagiosum infection. *Clin Pediatr (Phila).* 2009;48(2):161-165.
2. Coloe J, Morrell DS. Cantharidin use among pediatric dermatologists in the treatment of molluscum contagiosum. *Pediatr Dermatol*. 2009;26(4):405-408.
3. Han L, Sun Y, Pan Y-F, Ding H, Chen X, Zhang X. Cantharidin combined with chemotherapy for Chinese patients with metastatic colorectal cancer. *Asian Pacific J Cancer Prev*. 2014;15(24):10977-10979.
4. Jahnke MN, Hwang S, Griffith JL, Shwayder T. Cantharidin for treatment of facial molluscum contagiosum: a retrospective review. *J Am Acad Dermatol*. 2018;78(1):198-200.
5. Kollipara R, Ekhlassi E, Downing C, Guidry J, Lee M, Tyring SK. Advancements in pharmacotherapy for noncancerous manifestations of HPV. *J Clin Med*. 2015;4(5):832-846.
6. Levitt JO, Keeley BR, Phelps RG. Treatment of porokeratosis of Mibelli with cantharidin. *J Am Acad Dermatol*. 2013;69(5):e254-e255.
7. Mathes EFD, Frieden IJ. Treatment of molluscum contagiosum with cantharidin: a practical approach. *Pediatr Ann*. 2010;39(3):124-130.
8. Miller DM, Brodell RT. Human papillomavirus infection: treatment options for warts. *Am Fam Physician*. 1996;53(1):135-148.
9. Moye V, Cathcart S, Burkhart CN, Morrell DS. Beetle juice: a guide for the use of cantharidin in the treatment of molluscum contagiosum. *Dermatol Ther*. 2013;26(6):445-451.
10. Ormond CS. Cantharone, a cantharidin tincture as a useful agent in treating intractable plantar lesions. *J Am Podiatry Assoc*. 1962;52:427-430.
11. Panzer HM. Cantharidin-a useful agent in the local treatment of warts. *J Germantown Hosp*. 1961;2:82-86.
12. Pompei DT, Rezzadeh KS, Viola K V., et al. Cantharidin therapy: practice patterns and attitudes of health care providers. *J Am Acad Dermatol*. 2013;68(6):1045-1046.
13. Coskey RJ. Treatment of plantar warts in children with a salicylic acid-podophyllin-cantharidin product. *Pediatr Dermatol*. 1984;2(1):71-73.
14. Ramírez-Fort MK, Au S-C, Javed SA, Loo DS. Management of cutaneous human papillomavirus infection: pharmacotherapies. *Curr Probl Dermatol*. 2014;45:175-185.
15. Rodríguez-Martín M, de Paz NM, Ferrer PC, et al. Cantharidin: a well-tolerated and effective therapy for molluscum contagiosum in children. *J Pediatr Infect Dis*. 2011;6(2):121-123.
16. Ross GL, Orchard DC. Combination topical treatment of molluscum contagiosum with cantharidin and imiquimod 5% in children: a case series of 16 patients. *Australas J Dermatol*. 2004;45(2):100-102.
17. Schencking M, Kraft K. Cantharidin patches and intravenous administration of vitamin C in the

concomitant treatment of herpes zoster: a case report. *J Chinese Integr Med*. 2011;9(4):410-413.

18. Torbeck R, Pan M, de Moll E, Levitt J. Cantharidin: a comprehensive review of the clinical literature. *Dermatol Online J*. 2014;20(6).
19. Wong J, Phelps R, Levitt J. Treatment of acquired perforating dermatosis with cantharidin. *Arch Dermatol*. 2012;148(2):160-162.
20. Xiao Z, Wang C, Chen L, et al. Has aidi injection the attenuation and synergistic efficacy to gemcitabine and cisplatin in non-small cell lung cancer? A meta-analysis of 36 randomized controlled trials. *Oncotarget*. 2017;8(1):1329-1342.
21. Xiao Z, Wang C, Zhou M, et al. Clinical efficacy and safety of Aidi injection plus paclitaxel-based chemotherapy for advanced non-small cell lung cancer: a meta-analysis of 31 randomized controlled trials following the PRISMA guidelines. *J Ethnopharmacol*. 2019;228:110-122.
22. Dostrovsky A, Ticho A. A case of ocular leprosy treated with autoserum from cantharides blisters. *Int J Lepr*. 1949;17(1-2):43-47.
23. Epstein E. Cantharidin therapy for molluscum contagiosum in children. *J Am Acad Dermatol*. 2001;45(4):638.
24. Epstein E. Cantharidin treatment of mulluscum contagiosum. *Acta Derm Venereol*. 1989;69(1):91-92.
25. Epstein JH, Epstein WL. Cantharidin treatment of digital and periungual warts. *Calif Med*. 1960;93(1):11-12.
26. Epstein WL, Kligman AM. Treatment of warts with cantharidin. *AMA Arch Derm*. 1958;77(5):508–511.
27. Funt TR, Mehr KA. Cantharidin a valuable office treatment of mulluscum. *South Med J*. 1979;72(8):1019.
28. Funt TR. Cantharidin treatment of molluscum contagiosum. *Arch Dermatol*. 1961;83(186-187):2-3.
29. Akdemir O, Bilkay U, Tiftikcioglu YO, et al. New alternative in treatment of callus. *J Dermatol*. 2011;38(2):146-150.
30. Coloe Dosal J, Stewart PW, Lin J-A, Williams CS, Morrell DS. Cantharidin for the treatment of molluscum contagiosum: a prospective, double-blinded, placebo-controlled trial. *Pediatr Dermatol*. 2014;31(4):440-449.
31. Recanati MA, Kramer KJ, Maggio JJ, Chao CR. Cantharidin is superior to trichloroacetic acid for the treatment of non-mucosal genital warts: a pilot randomized controlled trial. *Clin Exp Obstet Gynecol*. 2018;45(3):383-386.
32. Robson KJ, Cunningham NM, Kruzan KL, et al. Pulsed-dye laser versus conventional therapy in the treatment of warts: a prospective randomized trial. *J Am Acad Dermatol*. 2000;43(2):275-280.
33. Saraogi P, Madan V. Pulsed-dye laser and topical cantharidin for the treatment of recalcitrant cutaneous warts. *Br J Dermatol*. 2016;175:115.
34. Ghonemy S. Treatment of recalcitrant plantar warts with long-pulsed Nd:YAG laser versus cantharidin–podophylline resin–salicylic acid. *J Cosmet Laser Ther*. 2017;19(6):347-352.

35. Guzman AK, Garelik JL, Cohen SR. Topical cantharidin revisted: a phase 2 study investigating a commercially-viable formulation of cantharidin (VP-102) for the treatment of molluscum contagiosum. *Pediatr Dermatol*. 2018;35(5):712.

36. Guzman AK, Schairer DO, Garelik JL, Cohen SR. Safety and efficacy of topical cantharidin for the treatment of pediatric molluscum contagiosum: a prospective, randomized, double-blind, placebo-controlled pilot trial. *Int J Dermatol*. 2018;57(8):1001-1006.

37. Hanna D, Hatami A, Powell J, et al. A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatr Dermatol*. 2006;23(6):574-579.

38. Kaçar N, Taşli L, Korkmaz S, Ergin Ş, Erdoğan BŞ. Cantharidin-podophylotoxin-salicylic acid versus cryotherapy in the treatment of plantar warts: a randomized prospective study. *J Eur Acad Dermatology Venereol*. 2012;26(7):889-893.

39. Kartal Durmazlar SP, Atacan D, Eskioglu F. Cantharidin treatment for recalcitrant facial flat warts: a preliminary study. *J Dermatolog Treat*. 2009;20(2):114-119.

40. López López D, Fernandez JMV, Iglesias MEL, et al. Safety and effectiveness of cantharidin–podophylotoxin–salicylic acid in the treatment of recalcitrant plantar warts. *Dermatol Ther*. 2016;29(4):269-273.

41. Meymandi SS, Vaseli MB, Alfatoonian M, Abroud F. Efficacy of cryotherapy combined with topical cantharidin application versus cryotherapy and placebo in the treatment of verruca vulgaris: a randomized, controlled clinical trial. *J Pakistan Assoc Dermatologists*. 2017;27(1):42-47.

42. Becerro de Bengoa Vallejo R, Losa Iglesias ME, Gómez-Martín B, Gómez RS, Crespo AS. Application of cantharidin and podophyllotoxin for the treatment of plantar warts. *J Am Podiatr Med Assoc*. 2008;98(6):445-450.

43. Rosenberg EW, Amonette RA, Gardner JH. Cantharidin treatment of warts at home. *Arch Dermatol*. 1977;113:1134.

44. Silverberg JI, Silverberg NB. Adjunctive trichloroacetic acid therapy enchances response to squaric acid response to verruca vulgaris. *J Drugs Dermatology*. 2012;11(10):1228-1230.

45. Silverberg NB, Sidbury R, Mancini AJ. Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol*. 2000;43(3):503-507.

Appendix 2. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **cantharidin**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

End of Block: Welcome Page

Start of Block: Cantharidin

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **cantharidin**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☐ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ☐ Unsure

Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for cantharidin? Please check all th... != Compounded drug product

Skip To: Q2 If What type(s) of product(s) do you use, prescribe, or recommend for cantharidin? Please check all th... = Compounded drug product

---

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for cantharidin? Please check all th... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **cantharidin** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **cantharidin** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q5 If Do you use compounded cantharidin as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded cantharidin as a single agent active ingredient, or as one active ingredient... = Combination

Q4. In which combination(s) do you use compounded **cantharidin**? Please check all that apply.

- ☐ Cantharidin 1% / Podophyllum resin 5% / Salicylic acid 30%
- ☐ Other (please describe) _____

Q5. For which, if any, diseases or conditions do you consider compounded **cantharidin** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **cantharidin** in medical practice guidelines or other resources?

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **cantharidin** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why) _____
- ○ Yes - I use it **LESS** often now (briefly describe why) _____
- ○ No - use has remained consistent

Q8. Why do you use compounded **cantharidin** instead of any FDA-approved drug product?

_____

Q9. Do you stock non-patient-specific compounded **cantharidin** in your practice location?

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded cantharidin in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded cantharidin in your practice location? = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **cantharidin**? Please check all that apply.

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **cantharidin**? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **cantharidin**? Please check all that apply.

- ☐ Convenience
- ☐ Emergencies
- ☐ Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded cantharidin? Please check all that apply. = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded cantharidin? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded cantharidin? Please check all that apply. = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **cantharidin** standard therapy?

_____

Q14. Does your specialty describe the use of **cantharidin** in medical practice guidelines or other resources?

_____

End of Block: Cantharidin

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ☐ Doctor of Medicine (MD)
- ☐ Doctor of Osteopathic Medicine (DO)
- ☐ Doctor of Medicine in Dentistry (DMD/DDS)
- ☐ Naturopathic Doctor (ND)
- ☐ Nurse Practitioner (NP)
- ☐ Physician Assistant (PA)
- ☐ Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ☐ No Board certification
- ☐ Allergy and Immunology
- ☐ Anesthesiology
- ☐ Cardiovascular Disease
- ☐ Critical Care Medicine
- ☐ Dermatology
- ☐ Emergency Medicine
- ☐ Endocrinology, Diabetes and Metabolism
- ☐ Family Medicine
- ☐ Gastroenterology
- ☐ Hematology
- ☐ Infectious Disease
- ☐ Internal Medicine
- ☐ Medical Toxicology
- ☐ Naturopathic Doctor
- ☐ Naturopathic Physician
- ☐ Nephrology
- ☐ Neurology
- ☐ Obstetrics and Gynecology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Otolaryngology
- ☐ Pain Medicine
- ☐ Pediatrics
- ☐ Psychiatry
- ☐ Rheumatology
- ☐ Sleep Medicine
- ☐ Surgery (please describe) _____
- ☐ Urology
- ☐ Other (please describe) _____

End of Block: Background Information