

Summary Report

Aluminum Chloride Hexahydrate

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

REVIEW OF NOMINATIONS	4
METHODOLOGY	4
Background information	4
Systematic literature review	5
Outreach to medical specialists and specialty organizations.....	7
Survey	7
CURRENT AND HISTORIC USE.....	9
Summary of background information.....	9
Summary of literature review.....	10
Summary of focus groups/interviews of medical experts and specialty organizations.....	17
Summary of survey results.....	19
CONCLUSION.....	21
APPENDICES	22
Appendix 1. References	22
Appendix 2. Survey instrument.....	32

Table of Tables

Table 1. Participating associations	7
Table 2. Associations that declined participation.....	8
Table 3. Currently approved products – US	9
Table 4. Currently approved products–select non-US countries and regions	9
Table 5. Types of studies	10
Table 6. Number of studies by country ^a	10
Table 7. Number of studies by combinations.....	12
Table 8. Dosage by indication – US	13
Table 9. Dosage by indication – non-US countries	14
Table 10. Compounded products – US.....	16
Table 11. Compounded products – non-US countries	16
Table 12. Overview of interviewee	17
Table 13. Characteristics of survey respondents	19
Table 14. Types of products used, prescribed, or recommended	19
Table 15. Compounded use of aluminum chloride in practice.....	19
Table 16. Indications for which aluminum chloride is considered a standard therapy	20
Table 17. Reasons for using compounded product instead of the FDA-approved products.....	20
Table 18. Change in frequency of compounded aluminum chloride usage over the past 5 years.....	20
Table 19. Do you stock non-patient specific compounded aluminum chloride in your practice?	20
Table 20. Questions related to stocking non-patient specific compounded aluminum chloride	21

REVIEW OF NOMINATIONS

Aluminum chloride hexahydrate (UNII code: HPN8MZW13M, 3CYT62D3GA) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society and Sincerus Florida, LLC for hyperhidrosis and as a hemostatic agent. The nominated formulations are a topical 20% solution and a 35% irrigation solution. Aluminum chloride hexahydrate was nominated for combination use in combination with additional active pharmaceutical ingredients (API), 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.
- Aluminum chloride will be compounded with hydrocortisone and additional active ingredients to reduce the potential for irritation from commercially available products.
- 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.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of aluminum chloride hexahydrate 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 aluminum chloride hexahydrate; name variations of aluminum chloride hexahydrate 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 aluminum chloride hexahydrate. 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 December 20, 2018. The search included a combination of ("aluminium chloride hexahydrate"[TIAB] OR "aluminium chloride"[TIAB] OR "aluminum chloride hexahydrate"[TIAB] OR "aluminum chloride"[TIAB] OR Drysol[TIAB] OR hexahydrate[TIAB]) AND (clinical[TIAB] OR treatment[TIAB] OR therapeutic*[TIAB] OR therapy[TIAB] OR sweat*[TIAB] OR hyperhidrosis[TIAB] OR antiperspirant[TIAB] OR dermat*[TIAB] OR perspir*[TIAB] OR hemosta*[TIAB] OR haemosta*[TIAB] OR bleed*[TIAB] OR hemato*[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 aluminum chloride hexahydrate or the implementation of aluminum chloride hexahydrate 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 aluminum chloride hexahydrate 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 aluminum chloride hexahydrate compared to alternative therapies.

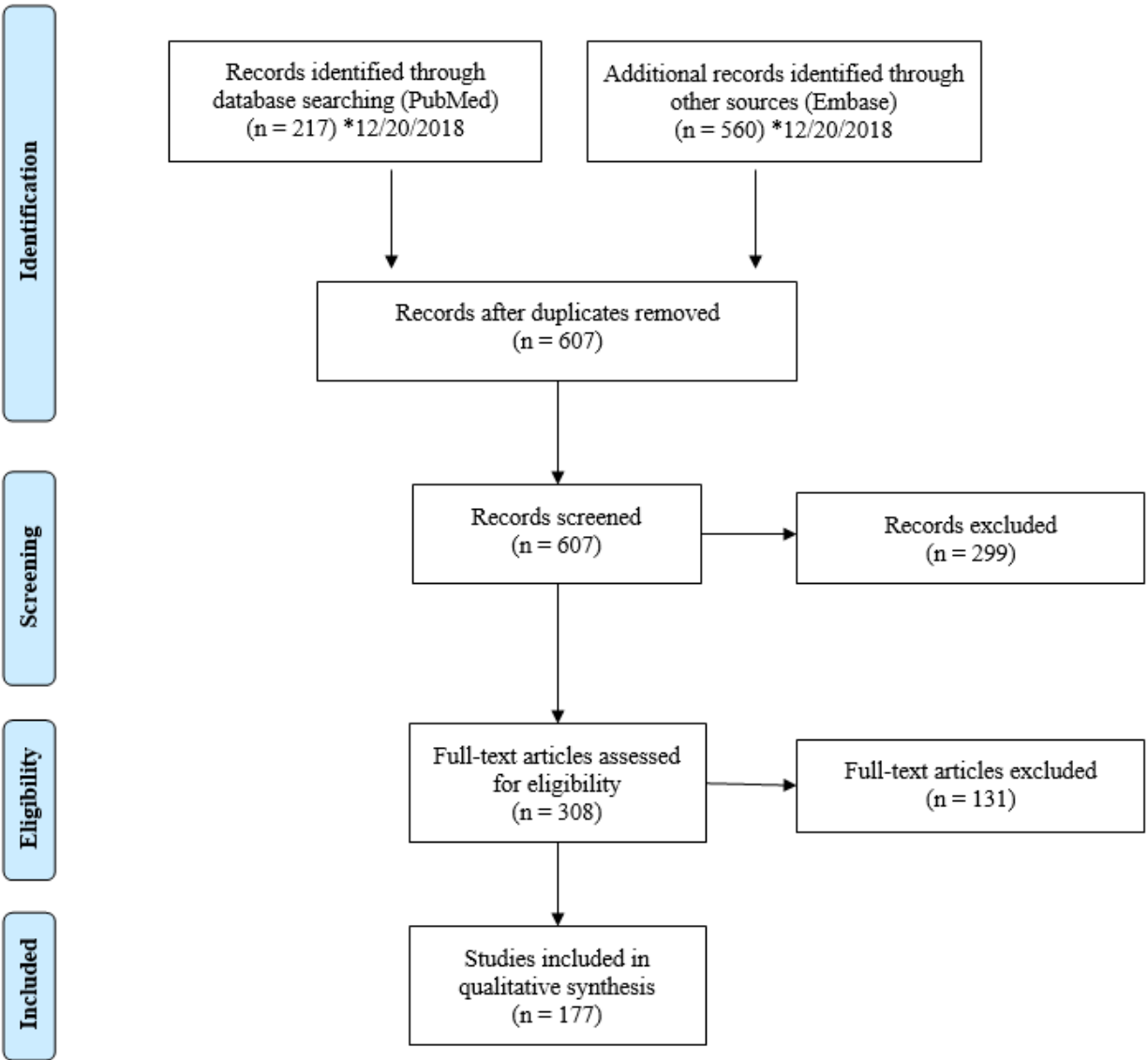
Results

Please refer to Figure 1.

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



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: 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 indications from the nominations and the results of the literature review, three (3) medical specialties that would potentially use aluminum chloride hexahydrate were identified: dermatology, infectious disease, and primary care. 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 an interview, of which one (1) accepted and zero (0) declined interviews. 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 primary care, identified from the nominations, 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. Infectious disease was addressed via Medicine organizations.

An online survey was created using Qualtrics® software (Provo, UT). The survey was distributed to seven (7) 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)
Primary Care	American Academy of Environmental Medicine (AAEM)

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
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Aluminum chloride hexahydrate is not available as an FDA-approved product.
- Aluminum chloride hexahydrate is available in various topical dosage forms as an OTC product in the US.
- There is a current United States Pharmacopoeia (USP) monograph for aluminum chloride hexahydrate.
- Aluminum chloride hexahydrate is available in Ireland and the UK.

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
Aluminum chloride hexahydrate	20%	Solution	Cutaneous, topical	Ireland	Pharmacy-only ^c	3/15/1982
				UK	Pharmacy-only ^c	8/31/1981

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

^aMedicine 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.

^bIf multiple approval dates and/or multiple strengths, then earliest date provided.

^cPharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Summary of literature review

- Total number of studies included: 177 studies (130 descriptive, 45 experimental, and 2 observational).
- Most of the studies were from the US (71).
- No study was identified as the nominated combination with hydrocortisone; 22 studies reported use in combination products.
- The most common indications for the use of aluminum chloride hexahydrate in the US were hyperhidrosis, hemostasis, pitted keratolysis, and epidermolysis bullosa. The most common indications from the non-US studies were hyperhidrosis, aquagenic keratoderma, gingival retraction, and hemostasis.
- Three (3) compounded products (3.125-25% solution and 20% gel) were identified from the US studies and five (5) compounded products (5-25% solution) were identified from the non-US studies.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive ¹⁻¹³⁰	130
Experimental ¹³¹⁻¹⁷⁵	45
Observational ^{176,177}	2

Table 6. Number of studies by country^a

Country	Number of Studies
Australia ^{55,90}	2
Belgium ^{50,173}	2
Brazil ¹²⁰	1
Canada ^{12,13,45,51,67,74,100,110,137}	9
China ^{129,168}	2
Denmark ^{18,138,143,147,149,150}	6
Egypt ¹³¹	1
Germany ^{11,49,68,76,107,118,123,144,169}	9
Iceland ¹³⁹	1
India ^{39,44,162,175}	4

Iran ^{134,151}	2
Italy ^{32,78,176}	3
Japan ^{35,54,75,112,125,128,174}	7
Jordan ¹³³	1
Lebanon ^{48,146}	2
Mexico ¹⁷⁷	1
Saudi Arabia ^{5,111}	2
Singapore ¹⁴⁵	1
South Africa ¹⁵⁸	1
South Korea ⁵⁹	1
Spain ^{9,19,33,34,84,155-157,164,172}	10
Sweden ¹⁰¹	1
Switzerland ¹³⁵	1
Taiwan ⁶⁶	1
The Netherlands ^{8,113}	2
Turkey ^{20,60-62,95,96,127,132}	8
UK ^{14,25,28,34,36,42,43,46,63,71,73,80,83,91,94,102,140,154,163,165}	20
US ^{1,6,7,10,15-17,21-24,26,27,29-31,37,38,40,41,47,52,53,56-58,64,69,70,72,77,79,81,82,85-89,92,93,97-99,103,104,106,108,109,114-117,119,121,122,124,126,136,141,142,148,152,153,159-161,166,167,170,171}	71
Multiple Countries <ul style="list-style-type: none"> • Canada, US⁶⁵ 	1
Total US ^b : 72	
Total non-US Countries ^b : 102	

^aStudies 2-4, 130 did not mention the country

^bStudy 65 counted in both US and non-US total

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Aluminum chloride hexahydrate 20% / Hydrocortisone	0
Others found in literature	Aluminum chloride 20% / Amitriptyline 10-20mg ²⁰	1
	Aluminum chloride hexahydrate / Kaolin (Expasyl) – paste ^{85,156,157,159}	4
	Aluminum chloride hexahydrate 15-55% / Salicylic acid 2-6% – gel ^{12,16,26,27,35,38,41,50,56,117,121,122,137,141}	14
	Aluminum chloride 50% / Silver nitrate 75% ⁷	1
	Aluminum chloride 20% / Talcum powder ⁵⁸	1
	Aluminum chloride hexahydrate 20% / Urea 20% – cream ⁵¹	1

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Hyperhidrosis ^{1,6,10,16,17,22-24,27,29,37,38,40,41,56,65,72,77,86,88,89,92,98,99,103,104,108,114,116,117,119,121,122,126,136,141,142,160,161,167,171}	–	1-35%	Gel, solution	Topical	2 days-1.5 years
					As needed
Hemostasis ^{7,21,30,31,52,53,64,79,85,109,159,170}	–	20-40%	Paste	Topical	Once
		5-50%	Solution		
Pitted keratolysis ^{87,93,97,115}	–	20%	Solution	Topical	–
Epidermolysis bullosa ^{57,69,70,106}	–	20%	Solution	Topical	2 weeks
Aquagenic keratoderma ^{81,124}	–	20%	Solution	Topical	3 months
Athlete’s foot/tinea pedis ¹⁵³	–	10-30%	Solution	Topical	1 week
					As needed
Frey’s syndrome ^{26,47}	–	20%	Gel, solution	Topical	–
Acne ¹⁴⁸	–	3.125-25%	Solution	Topical	2 weeks-more than 32 weeks
Chromhidrosis ¹⁵	–	20%	Solution	Topical	–
Erythrasma ⁹⁷	–	20%	Solution	Topical	–
Folliculitis ¹⁶⁶	–	6.25%	Solution	Topical	At most 1 year
Plantar wart ⁸²	–	6%	Solution	Topical	7-10 days
Reduction of foot blisters ¹⁵²	–	20%	Solution	Topical	5 days

Symmetric lividities ⁵⁸	–	20%	–	Topical	5 months
Trichomycosis axillaris ⁹⁷	–	20%	Solution	Topical	–

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Hyperhidrosis ^{2-5,8,11-13,18-20,25,32,33,35,36,42-46,49,50,55,59,61,65,67,73-76,78,80,83,90,91,94,100,101,107,110,120,123,137,138,140,143,145,146,149-151,154,158,162-165,168,169,172-174}	–	1-30%	–	Topical	4 days-6 weeks
	5 µL	1-50%	Solution		Once-At least 1 year
	–	15-55%	Cream, gel, lotion, ointment, spray		As needed
	–	15-55%	Cream, gel, lotion, ointment, spray		2 weeks-6 months
Aquagenic keratoderma ^{9,32,34,39,51,54,60,62,66,84,95,96,102,111,129,177}	–	15-20%	Cream, gel, lotion, spray, solution	Topical	1 week-3 months
					As needed
Gingival retraction ^{131-133,139}	–	25%	–	Topical	Once
		14-25%	Paste		
Hemostasis ^{71,130,155-157}	–	–	Paste	Topical	–
Frey’s syndrome ^{14,49}	–	20%	Solution	Topical	5-31 months
Pitted keratolysis ^{68,113}	–	20%	Solution	Topical	–
Acne vulgaris ¹⁴⁷	–	6.25%	–	Topical	8 weeks

Bromhidrosis ⁴⁸	–	12.5%	–	Topical	–
Chromhidrosis ^{105,127}	–	20%	Solution	Topical	–
Eccrine hidrocystoma ¹³⁴	–	15%	Solution	Topical	4 weeks
Eccrine nevus ²⁸	–	–	–	Topical	–
Erythema papulatum centrifugum ¹¹²	–	–	–	Topical	–
Gram-negative bacterial toe web infection ¹¹⁸	–	–	–	Topical	–
Gustatory sweating ¹²⁸	1 mL/day	20%	–	Topical	–
Inherited epidermolysis bullosa	–	20%	Solution	Topical	4 weeks
Mucositis ¹⁷⁵	–	–	–	Topical	–
Paronychia and pyogenic granuloma ¹⁷⁶	–	5%	Gel	Topical	–
Ross syndrome ⁴⁹	–	–	–	–	–
Skin protection ¹⁴⁴	–	5%	Solution	Topical	Thrice
Sweating, erythema, blistering ¹³⁵ <i>*specific to skin problems in sugar artists</i>	–	10%	Solution	Topical	4 weeks
Symmetric lividities ¹²⁵	–	20%	Solution	Topical	2 weeks

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Hyperhidrosis ¹⁶⁷	1975	<ul style="list-style-type: none"> Aluminum salt crystals dissolved in absolute ethyl alcohol at room temperature for 3 weeks until a clear viscous solution reached 	Solution	25%
Acne ¹⁴⁸	1978	<ul style="list-style-type: none"> Dissolution of 25% aluminum chloride hexahydrate in anhydrous (200 proof) ethanol for 21 days at 20°C 	Solution	3.125-25%
Frey's syndrome ²⁶	2006	<ul style="list-style-type: none"> Dissolved in a 4% salicylic acid gel base 	Gel	20%

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Hyperhidrosis ^{138,140,154,165}	<ul style="list-style-type: none"> Dissolved in absolute ethanol at room temperature for about 3-4 weeks^{138,140,165} 	Solution	20-25%
	<ul style="list-style-type: none"> Dissolved in absolute alcohol using a magnetic stirrer at room temperature for 2-3 days¹⁵⁴ 		20%
Skin protection ¹⁴⁴	<ul style="list-style-type: none"> Mixed with purified water and isopropyl alcohol 	Solution	5%

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 Aluminum Chloride Hexahydrate	Interview Summary Response
DER_05	MD	Dermatology Dermatology/Immunology	Independent Consultant	Not specified	<ul style="list-style-type: none"> • There is a need for office stock especially as a cauterizing agent. • Availability of other concentrations besides 20% is potentially helpful • Good risk-benefit ratio and therapeutic index

Abbreviation: MD, Doctor of Medicine.

Indications:

- The interviewee stated that in the office setting, they are more likely using aluminum chloride as a cauterization agent (stops the bleeding).
- Also used for hyperhidrosis but typically, the prescriber would write a prescription for hyperhidrosis. If a higher concentration is needed, they could write a patient specific prescription for the compounding pharmacy.

Aluminum chloride versus aluminum chloride hexahydrate

- The interviewee does not know enough about how soluble aluminum chloride compared to the hexahydrate salt form may be.
- Maybe at higher concentrations, the salt is potentially more soluble.

Experience with aluminum chloride

- The interviewee used to use a 35% solution in the hospital-based setting.
- Drysol is the commercially available aluminum chloride at 20%.

- Higher concentrations are slightly more effective as a caustic agent. Lower concentrations take more time and pressure to provide the desired effect.
- The interviewee also stated, “with the population that we have, patients who are aging, patients who may or may not be taking an aspirin a day. So their platelets are not quite working right. I think the availability of other concentrations is really, potentially, helpful.”

Need for office stock

- The interviewee expressed that there is a need for office stock.
- Aluminum chloride may be used by dermatologists or other providers completing simple skin procedures.
 - An example given by the interviewee: “So if you're doing a shave biopsy...because you think somebody has seborrheic keratosis, but you want to rule out skin cancer. Or, it's a skin cancer. You can use aluminum chloride on a Q-tip, on the base of the wound, after you remove that small skin sample. And it cauterizes the vessels.”
- There is no current commercially available product that matches the high concentration (35%) the interviewee had previously used in practice.
- Overall, the interviewee expressed that office stock aluminum chloride would be a “very inexpensive cost-effective, low-risk solution that can be deployed in a very safe way without people getting into any trouble with it. I'm not worried about this one.”

Summary of survey results

Table 13. Characteristics of survey respondents [4 people responded to the survey]

Board Certification	MD	No Response
Dermatology	1	0
No Board Certification	0	0
No Response	0	3

Abbreviation: Abbreviation: MD, Doctor of Medicine.

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

Types of Products	Respondents, n (N=4^a)
Compounded	2
FDA-approved	1
OTC	0
Dietary	0
Unsure	1
No response	0

^aOut of four (4) respondents, four (4) reported using, prescribing, or recommending aluminum chloride hexahydrate products.

Table 15. Compounded use of aluminum chloride in practice^a

Indication^b	Strength	Dosing frequency	Dosage Form^b	ROA	Duration of Treatment	Patient Population
“Used in the office for hemostasis with tangential excision or biopsies”	20%	Once	“in anhydrous alcohol”	Topical	Once	Adult/children; male and female

Abbreviation: ROA, route of administration.

^aOne (1) respondent.

^bQuotations are direct words from respondents.

Table 16. Indications for which aluminum chloride is considered a standard therapy

Indication	Standard therapy		
	Compounded, n (N=2)	Non-compounded, n (N=1)	Unsure, n (N=1)
Other ^a	1	0	0
No response	1	1	1

^aOne (1) respondent replied, “none, used for hemostasis in surgery.”

Table 17. Reasons for using compounded product instead of the FDA-approved products

Reasons
“Superior results and ease of use”

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

	Respondents, n (N=2)
No—use has remained consistent	0
Yes—I use it LESS often now	0
Yes—I use it MORE often now <ul style="list-style-type: none"> • “superior cosmetic result when used for hemostasis compared to electrodesiccation” 	1
No response	1

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

	Respondents, n (N=2)
No	0
Yes ^a	1
No response	1

^aOne (1) respondent reports stocking non-patient-specific compounded aluminum chloride hexahydrate in the physician office and obtains it from a medical wholesaler for daily hemostasis use.

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

No additional survey respondents provided this information

CONCLUSION

Aluminum chloride hexahydrate (UNII code: 3CYT62D3GA) was nominated for inclusion on the 503B Bulks List for hyperhidrosis and as a hemostatic agent. The nominated formulations are a topical 20% solution and a 35% irrigation solution. This substance was also nominated for use in combination with hydrocortisone.

Aluminum chloride hexahydrate is available in various topical OTC dosage forms in the US and has a current USP monograph. Out of the foreign medicine registries searched, aluminum chloride hexahydrate is available in Ireland and the UK.

From the literature review conducted, the most common indications in the US were hyperhidrosis, hemostasis, pitted keratolysis, and epidermolysis bullosa. The most common indications from the non-US studies were hyperhidrosis, aquagenic keratoderma, gingival retraction, and hemostasis. Three (3) compounded products (3.125-25% solution and 20% gel) were identified from the US studies and five (5) compounded products (5-25% solution) were identified from the non-US studies. No study was identified with the nominated combination with hydrocortisone, however, 22 studies reported use in combinations.

From the interview conducted, the interviewee expressed that there is a need for office stock as a cauterizing agent. Even though aluminum chloride is commercially available as a 20% product, the interviewee thinks the availability of other concentrations would be helpful. There is a good risk-benefit ratio and therapeutic index for aluminum chloride, and the interviewee has previously used aluminum chloride as a 35% solution in a hospital-based setting.

From the survey responses, four (4) out of four (4) respondents used aluminum chloride. Two (2) respondents use compounded aluminum chloride. One (1) respondent reported using aluminum chloride for hemostasis in the office with “tangenital excision or biopsies.” For office stock, one (1) respondent reported stocking compounded aluminum chloride in the physician office for daily hemostasis use.

APPENDICES

Appendix 1. References

1. Drysol for treatment of hyperhidrosis. *Med Lett Drugs Ther.* 1977;19(4):20.
2. Aluminum chloride for hyperhidrosis. *Drug Ther Bull.* 1981;19(26):101-2.
3. No sweat - Hyperhidrosis can be controlled. *Drugs Ther Perspect.* 2004;20(10):17-20.
4. Tailor therapy according to patient needs and anatomical site when treating primary hyperhidrosis. *Drugs Ther Perspect.* 2012;28(6):19-22.
5. Albadrani A. Clonidine is effective for the treatment of primary idiopathic hyperhidrosis and hot flushes: A case report. *J Med Case Reports.* 2017;11(1).
6. Altman RS, Schwartz RA. Treatment of palmo-plantar hyperhidrosis. *Acta Dermatovenerol Alp Pannonica Adriat.* 2002;11(1):21-24.
7. Alvarez S, Asztalos L, Tung-Hahn E, Peterson A, Tung R. Flexible blade decortication and pulsed dye laser for the treatment of rhinophyma: A case series. *J Am Acad Dermatol.* 2017;76(6):AB141.
8. Amini M, Harmsze AM, Tupker RA. Patient's estimation of efficacy of various hyperhidrosis treatments in a Dermatological clinic. *Acta Derm Venereol.* 2008;88(4):356-362.
9. Bagazgoitia L, Pérez-Carmona L, Salguero I, Harto A, Jaén P. Aquagenic keratoderma: Successful treatment with botulinum toxin. *Dermatol Surg.* 2010;36(3):434-436.
10. Baumgartner FJ. Surgical approaches and techniques in the management of severe hyperhidrosis. *Thorac Surg Clin.* 2008;18(2):167-181.
11. Bechara FG, Sand M, Moussa G, et al. Treatment of unilateral compensatory sweating after endoscopic thoracic sympathectomy for general hyperhidrosis with botulinum toxin A. *Dermatol Surg.* 2006;32(5):745-748.
12. Benohanian A. Treatment of recalcitrant plantar hyperhidrosis with type-A botulinum toxin injections and aluminum chloride in salicylic acid gel. *Dermatol Online J.* 2008;14(2).
13. Benohanian A, Boudjikianian A, Paylan Y. Palmar and plantar hyperhidrosis: A practical management algorithm. *Therapy.* 2007;4(3):279-283.
14. Black MJ, Gunn A. The management of Frey's syndrome with aluminium chloride hexahydrate antiperspirant. *Ann R Coll Surg Engl.* 1990;72(1):49-52.
15. Blalock TW, Crowson AN, Danford B. A case of generalized red sweating. *Dermatol Online J.* 2014;21(3).
16. Bohaty BR, Hebert AA. Special Considerations for Children with Hyperhidrosis. *Dermatol Clin.* 2014;32(4):477-484.
17. Bohn P, Sternbach H. Topical aluminum chloride for social phobia-related hyperhidrosis [6]. *Am J Psychiatry.* 1996;153(10):1368.
18. Boje Rasmussen H, Ullman S. Naevus sudoriferus (local eccrine hyperhidrosis). *J Eur Acad Dermatol Venereol.* 1997;9(3):273-275.

19. Borrego L, López-Estebarez JL, Vicente J, Sols M, Pinedo F. Focal recurrent episodic hyperhidrosis on the forearm. *Arch Dermatol*. 2001;137(9):1241-1246.
20. Boyvat A, Piskin G, Erdi H. Idiopathic unilateral localized hyperhidrosis [16]. *Acta Derm Venereol*. 1999;79(5):404-405.
21. Chen DL, Carlson EO, Fathi R, Brown MR. Undermining and hemostasis. *Dermatol Surg*. 2015;41(10):S201-S215.
22. Cheshire WP, Freeman R. Disorders of Sweating. *Semin Neurol*. 2003;23(4):399-406.
23. Childress K, Brown O, Bercaw-Pratt J. Hyperhidrosis of the vulva. *J Pediatr Adolesc Gynecol*. 2016;29(2):189.
24. Childress KJ, Brown O, Bercaw-Pratt J. Inguinal Hyperhidrosis: Case Report of an Uncommon Cause of Vaginitis. *J Pediatr Adolesc Gynecol*. 2018;31(4):420-421.
25. Clark C. Sweating and hyperhidrosis. *Pharm J*. 2006;276(7406):757-760.
26. Clayman MA, Clayman SM, Seagle MB. A review of the surgical and medical treatment of frey syndrome. *Ann Plast Surg*. 2006;57(5):581-584.
27. Cohen JL, Cohen G, Solish N, Murray CA. Diagnosis, Impact, and Management of Focal Hyperhidrosis: Treatment Review Including Botulinum Toxin Therapy. *Facial Plast Surg Clin North Am*. 2007;15(1):17-30.
28. Dua J, Grabczynska S. Eccrine nevus: Case report in a child. *J Am Acad Dermatol*. 2013;68(4):AB173.
29. Dworin A, Sober AJ. Unilateral segmental hyperhidrosis. Response to 20% aluminum chloride solution and plastic wrap. *Arch Dermatol*. 1978;114(5):770-771.
30. Elledge D. Effective hemostasis and tissue management. *Dent Today*. 2010;29(10):150-153.
31. Epstein E, Long C, Motley R, Holt P. Treatment of basal cell papillomas [2]. *Br J Dermatol*. 1995;133(3):492-493.
32. Errichetti E, Piccirillo A. Aquagenic keratoderma treated with tap water iontophoresis. *Indian J Dermatol*. 2015;60(2):212.
33. Fernandez G, Armijo M. Unilateral facial circumscribed hyperhidrosis. *Acta Derm Venereol*. 1985;65(5):445-447.
34. Flann S, Pembroke A. A localized form of aquagenic syringal acrokeratoderma: Viewpoints in dermatology • Correspondence. *Clin Exp Dermatol*. 2010;35(4):e147-e148.
35. Fujimoto T. Pathophysiology and Treatment of Hyperhidrosis. In. Vol 512016:86-93.
36. Ganeshmoorthy J, Saravanapavananthan T. A case of hyperhidrosis successfully treated with 20% aluminium chloride hexahydrate in 95% ethyl alcohol. *Singapore Med J*. 1990;31(1):85-86.
37. Gee S, Yamauchi PS. Nonsurgical Management of Hyperhidrosis. *Thorac Surg Clin*. 2008;18(2):141-155.
38. Gelbard CM, Epstein H, Hebert A. Primary pediatric hyperhidrosis: A review of current treatment options. *Pediatr Dermatol*. 2008;25(6):591-598.

39. Ghosh SK, Agarwal M, Ghosh S, Dey AK. Aquagenic palmar wrinkling in two Indian patients with special reference to its dermoscopic pattern. *Dermatol Online J.* 2015;21(6).
40. Glaser DA. Need help for hyperhidrosis? No sweat! *Consultant.* 2006;46(14):1542.
41. Gordon JRS, Hill SE. Update on pediatric hyperhidrosis. *Dermatol Ther.* 2013;26(6):452-461.
42. Grice K. Treating hyperhidrosis. *Practitioner.* 1988;232(1454 I):953-956.
43. Griffiths WAD. The treatment of idiopathic hyperhidrosis. *Prescr J.* 1984;24(2):38-41.
44. Gupta V, Bhatia S, Arava S, Sharma VK. A hairy port-wine stain with overlying hyperhidrosis on the thigh of a child. *Int J Dermatol.* 2017;56(12):1349-1351.
45. Haider A, Solish N. Focal hyperhidrosis: Diagnosis and management. *Can Med Assoc J.* 2005;172(1):69-75.
46. Halford J, Hunt L, Millington G. A patient's journey: Hyperhidrosis. *BMJ (Online).* 2009;338(7700):942-943.
47. Harper KE, Spielvogel RL. Frey's syndrome. *Int J Dermatol.* 1986;25(8):524-526.
48. Helou J, Haber R, Kechichian E, Tomb R. A case of generalized bromhidrosis following whole-body depilatory laser. *J Cosmet Laser Ther.* 2015;17(6):318-320.
49. Hölzle E. Topical pharmacological treatment. *Curr Probl Dermatol.* 2002;30((Hölzle E.) Klinik für Dermatologie und Allergologie, Städtische Kliniken Oldenburg, Deutschland.):30-43.
50. Hoorens I, Ongenaes K. Primary focal hyperhidrosis: Current treatment options and a step-by-step approach. *J Eur Acad Dermatol Venereol.* 2012;26(1):1-8.
51. Houle MC, Al Dhaybi R, Benohanian A. Unilateral aquagenic keratoderma treated with botulinum toxin A. *J Dermatol Case Rep.* 2010;4(1):1-5.
52. Howe N, Cherpelis B. Obtaining rapid and effective hemostasis: Part I. Update and review of topical hemostatic agents. *J Am Acad Dermatol.* 2013;69(5):659.e651-659.e617.
53. Hwa C, Kovich OI, Stein JA. Achieving hemostasis after nail biopsy using absorbable gelatin sponge saturated in aluminum chloride. *Dermatol Surg.* 2011;37(3):368-369.
54. Ibusuki C, Oka M, Fukunaga A, Kunisada M, Nishigori C. Unilateral aquagenic wrinkling of the palms with a peculiar clinical course. *Eur J Dermatol.* 2012;22(5):679-680.
55. Isaacs F. Excessive sweating: Causes and what to do about it. *Mod Med Aust.* 1998;41(11):30-34.
56. Jacobs AA, Desai A, Markus R. Don't sweat hyperhidrosis: A review of current treatment. *Cosmetic Dermatology.* 2005;18(10):725-731.
57. Jennings JL. Aluminum chloride hexahydrate treatment of localized epidermolysis bullosa. *Arch Dermatol.* 1984;120(10):1382.
58. Kearse HL, Nagy R. Symmetric lividities--therapy with aluminum chloride solution. *J Am Acad Dermatol.* 1986;15(3):539-540.
59. Kim JM, Seo SD, Kim YW, Hwang YH. Contralateral hyperhidrosis in anterior thalamic infarction. *Clin Auton Res.* 2014;24(6):311-313.
60. Kocatürk E, Kavala M, Büyükbabani N, Türkoğlu Z. Whitish papules on the palm. *Int J Dermatol.* 2007;46(7):736-737.

61. Köse O, Baloglu H. Idiopathic unilateral circumscribed hyperhidrosis. *Int J Dermatol*. 1997;36(3):209-210.
62. Kutlubay Z, Engin B, Baglam S, Khatib R, Demirkesen C, Aydemir EH. Case report: Treatment failure in a case of aquagenic syringeal acrokeratoderma. *J Cosmet Laser Ther*. 2015;17(4):224-226.
63. Langan SM, Williams HC. A systematic review of randomized controlled trials of treatments for inherited forms of epidermolysis bullosa. *Clin Exp Dermatol*. 2009;34(1):20-25.
64. Larson PO. Topical hemostatic agents for dermatologic surgery. *J Dermatol Surg Oncol*. 1988;14(6):623-632.
65. Lear W, Kessler E, Solish N, Glaser DA. An epidemiological study of hyperhidrosis. *Dermatol Surg*. 2007;33(SUPPL. 1):S69-S75.
66. Lee HC, Tsai TF. Aquagenic syringeal acrokeratoderma. *Dermatologica Sinica*. 2008;26(3):145-150.
67. Leung AKC, Barankin B. What's causing this teenager's profusely sweaty palms? *Consultant*. 2018;58(3):113-115+118.
68. Levy JA. Common bacterial dermatoses: Protecting competitive athletes. *Physician Sportsmed*. 2004;32(6):33-39+47.
69. Lin AN. Management of patients with Epidermolysis bullosa. *Dermatol Clin*. 1996;14(2):381-387.
70. Mailler EA, Adams BB. The wear and tear of 26.2: Dermatological injuries reported on marathon day. *Br J Sports Med*. 2004;38(4):498-501.
71. Mc Goldrick N, Ross C, Nelson J. Trial finds better haemostasis with aluminium chloride during periapical surgery. *Evid Based Dent*. 2017;18(2):50-51.
72. McConaghy JR, Fosselman D. Hyperhidrosis: Management options. *Am Fam Physician*. 2018;97(11):729-734.
73. Morris-Jones R. Neural control of sweat secretion: a review of the neurology and current treatment options for hyperhidrosis. *Br J Dermatol*. 2018;178(6):1233-1234.
74. Murray CA, Cohen JL, Solish N. Treatment of focal hyperhidrosis. *J Cutan Med Surg*. 2007;11(2):67-77.
75. Nakahigashi K, Nomura T, Miyachi Y, Kabashima K. Reduction of skin pH during treatment for palmoplantar hyperhidrosis: A conjecture on the role of ph-regulated water channel, i.e. aquaporin. *Case Rep Dermatol*. 2013;5(1):126-128.
76. Naumann M, Hamm H, Kinkelin I, Reiners K. Botulinum toxin type A in the treatment of focal, axillary and palmar hyperhidrosis and other hyperhidrotic conditions. *Eur J Neurol*. 1999;6(SUPPL. 4):S111-S115.
77. Newman CC, Litin SC, Bundrick JB. Clinical Pearls in Dermatology 2017. *Dis Mon*. 2017;63(7):165-175.
78. Paliogiannis P, Marrosu A, Attene F, Trignano M, Scognamillo F. An unusual case of excessive sweating affecting the right upper limb after bilateral endoscopic thoracic sympathectomy for

- primary palmar hyperhidrosis: Recurrence or compensatory hyperhidrosis? *Eur Surg - Acta Chir Austriaca*. 2014;46(4):169-172.
79. Palm MD, Altman JS. Topical hemostatic agents: A review. *Dermatol Surg*. 2008;34(4):431-445.
 80. Pardy BJ. Hyperhidrosis. *Current Practice in Surgery*. 1991;3(4):218-221.
 81. Park L, Khani C, Tamburro J. Aquagenic wrinkling of the palms and the potential role for genetic testing. *Pediatr Dermatol*. 2012;29(3):237-242.
 82. Pechman KJ. Does acyclovir have an adjunctive role in plantar wart therapy? *Cleve Clin Q*. 1983;50(2):213.
 83. Piercy J. 10-Minute consultation: Hyperhidrosis. *Br Med J*. 2005;330(7500):1127.
 84. Pinero Saavedra M, Prados Castano M, Ortega-Camarero M, Leguisamo Milla S. Aquagenic wrinkling of the palms associated with immunoglobulin A deficiency: A case report. *Allergy Eur J Allergy Clin Immunol*. 2012;67((Pinero Saavedra M.; Prados Castano M.; Ortega-Camarero M.; Leguisamo Milla S.) Allergy Department, Virgen del Rocio University Hospital, Sevilla, Spain):557-558.
 85. Poss S. An innovative tissue-retraction material. *Compend Contin Educ Dent Jamesburg NJ*. 2002;23(1 Suppl):13-17; quiz 18.
 86. Quatralo RP. The mechanism of antiperspirant action. *Cosmetics and Toiletries*. 1985;100(12):23-26.
 87. Ramsey ML. Pitted keratolysis: A common infection of active feet. *Physician Sportsmed*. 1996;24(10):51-56.
 88. Reisfeld R, Berliner KI. Evidence-Based Review of the Nonsurgical Management of Hyperhidrosis. *Thorac Surg Clin*. 2008;18(2):157-166.
 89. Robb-Nicholson C. By the way, doctor. I seem to sweat a great deal from my hands and underarms, more than my friends do. Sometimes I can't write or shake hands because my palms are dripping with sweat. Is there anything I can do about this embarrassing problem? *Harv Womens Health Watch*. 2005;13(1):8.
 90. Roberts H, Dolianitis C, Sinclair R. Assessing, investigating and managing hyperhidrosis. *Med Today*. 2007;8(9):47-55.
 91. Rowland Payne CME, Doe PT. Liposuction for axillary hyperhidrosis. *Clin Exp Dermatol*. 1998;23(1):9-10.
 92. Sato K, Ohtsuyama M, Samman G. Eccrine sweat gland disorders. *J Am Acad Dermatol*. 1991;24(6 I):1010-1014.
 93. Sedgwick PE, Dexter WW, Smith CT. Bacterial Dermatoses in Sports. *Clin Sports Med*. 2007;26(3):383-396.
 94. Segal-Hall GM, Smith P, Haworth AE. A case of isolated axillary hyperhidrosis successfully treated topically with 1% glycopyrronium cream [8]. *Clin Exp Dermatol*. 2006;31(6):825.
 95. Sezer E, Durmaz EÖ, Çetin E, Sahin S. Permanent treatment of aquagenic syringal acrokeratoderma with endoscopic thoracic sympathectomy. *Indian J Dermatol Venereol Leprol*. 2015;81(6):648-650.

96. Sezer E, Erkek E, Duman D, Şahin S, Çetin E. Dermatoscopy as an adjunctive diagnostic tool in aquagenic syringal acrokeratoderma. *Dermatology*. 2012;225(2):97-99.
97. Shelley WB, Shelley ED. Coexistent erythrasma, trichomycosis axillaris, and pitted keratolysis: An overlooked corynebacterial triad? *J Am Acad Dermatol*. 1982;7(6):752-757.
98. Shelley WB, Shelley ED. Recalcitrant unilateral infection associated with congenital leg hypertrophy cleared by control of hyperhidrosis. *Cutis*. 1984;33(3):281-282.
99. Simon HB. On call. Compared to the problems your readers ask about, my issue may seem silly. But I hope you'll give me some advice, since it really is very annoying. I'm troubled by excessive sweating. *Harv Mens Health Watch*. 2011;15(11):8.
100. Solish N, Bertucci V, Dansereau A, et al. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: Recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatol Surg*. 2007;33(8):908-923.
101. Stenquist B. Axillary hyperhidrosis: A simple surgical procedure. *J Dermatol Surg Oncol*. 1985;11(4):388-391.
102. Stewart LC, Doe SJ, Bourke SJ, Leech S. Aquagenic palmar wrinkling as a presenting feature of cystic fibrosis gene dysfunction. *Clin Exp Dermatol*. 2009;34(8):e647-e649.
103. Stolman LP. Treatment of Hyperhidrosis. *Dermatol Clin*. 1998;16(4):863-867.
104. Stolman LP. In hyperhidrosis (excess sweating), look for a pattern and cause. *Cleve Clin J Med*. 2003;70(10):896-898.
105. Tato BP, Martínez EZ, Albusua BS, et al. Facial and axillary apocrine chromhidrosis. *Dermatol Online J*. 2012;18(3):13.
106. Tkach JR. Treatment of recurrent bullous eruption of the hand and feet (Weber-Cockayne disease) with topical aluminum chloride. *J Am Acad Dermatol*. 1982;6(6):1095-1096.
107. Tögel B, Greve B, Raulin C. Current therapeutic strategies for hyperhidrosis: A review. *Eur J Dermatol*. 2002;12(3):219-223.
108. Torch EM. Remission of facial and scalp hyperhidrosis with clonidine hydrochloride and topical aluminum chloride. *South Med J*. 2000;93(1):68-69.
109. Trizna Z, Tyring SK, Wagner RF. Extraordinary delayed bleeding occurring after shave excision [3]. *J Am Acad Dermatol*. 2001;44(3):545.
110. Turchin I, Barankin B. Dermacase: Profuse sweating on the palms, soles, and axillae. *Can Fam Physician*. 2005;51(APR.):503-506.
111. Turkmani MG, Al-Hussain AH. Aquagenic Wrinkling of the Palms, two new cases from Saudi Arabia. *J Dermatol Dermatol Surg*. 2015;19(1):69-71.
112. Ueda C, Makino T, Mizawa M, Shimizu T. Erythema papulatum centrifugum: A sweat-related dermatitis. *J Am Acad Dermatol*. 2013;69(2):e103-e105.
113. Van Der Snoek EM, Ekkelenkamp MB, Suykerbuyk JCCW. Pitted keratolysis; Physicians' treatment and their perceptions in Dutch army personnel. *J Eur Acad Dermatol Venereol*. 2013;27(9):1120-1126.
114. Venman RL, Sato K. Hyperhidrosis. *J Am Med Assoc*. 1991;265(5):651.

115. Vlahovic TC. Dermatologic Concerns of the Lower Extremity in the Pediatric Patient. *Clin Podiatr Med Surg.* 2016;33(3):367-384.
116. Vlahovic TC, Dunn SP, Blau JC, Gauthier C. Injectable botulinum toxin as a treatment for plantar hyperhidrosis: A case study. *J Am Podiatr Med Assoc.* 2008;98(2):156-159.
117. Walling HW, Swick BL. Treatment options for hyperhidrosis. *Am J Clin Dermatol.* 2011;12(5):285-295.
118. Weidner T, Tittelbach J, Illing T, Elsner P. Gram-negative bacterial toe web infection – a systematic review. *J Eur Acad Dermatol Venereol.* 2018;32(1):39-47.
119. White JW. Treatment of Primary Hyperhidrosis. *Mayo Clin Proc.* 1986;61(12):951-956.
120. Wolosker N, Milanez de Campos JR, Fukuda JM. Management of Compensatory Sweating After Sympathetic Surgery. *Thorac Surg Clin.* 2016;26(4):445-451.
121. Woolery-Lloyd H, Valins W. Aluminum chloride hexahydrate in a salicylic acid gel: A novel topical agent for hyperhidrosis with decreased irritation. *J Clin Aesthet Dermatol.* 2009;2(6).
122. Woolery-Lloyd H, Valins W. Aluminum chloride hexahydrate in a salicylic acid gel base: A case series of combination therapy with botulinum toxin type a for moderate to severe hyperhidrosis. *Cutis.* 2011;88(1):43-45.
123. Wörle B, Rapprich S, Heckmann M. Definition and treatment of primary hyperhidrosis. *JDDG - J Ger Soc Dermatol.* 2007;5(7):625-628.
124. Yan AC, Aasi SZ, Alms WJ, et al. Aquagenic palmoplantar keratoderma. *J Am Acad Dermatol.* 2001;44(4):696-699.
125. Yanagi T, Sato-Matsumura KC, Nomura Y. Ultrasonography detects symmetrical lividities of the soles of the feet: A non-hyperhidrosis case treated with AlCl₃ solution. *Int J Dermatol.* 2013;52(9):1151-1153.
126. Yang CS, Teeple M, Muglia J, Robinson-Bostom L. Inflammatory and glandular skin disease in pregnancy. *Clin Dermatol.* 2016;34(3):335-343.
127. Yöntem A, Kör D, Hızlı-Karabacak B, Karakaş M, Önenli-Mungan N. Blue-colored sweating: Four infants with apocrine chromhidrosis. *Turk J Pediatr.* 2015;57(3):290-293.
128. Yoshimura H, Tobita T, Kumakiri M, Sano K. Gustatory sweating in the submandibular region following neck dissection: A case with thermographic evaluation and review of the literature. *J Oral Maxillofac Surg.* 2012;70(11):e667-e673.
129. Zhang R, Zhu WY, Yu Y. Aquagenic acrokeratoderma in a 5-year-old boy. *Eur J Pediatr Dermatol.* 2009;19(4):203-206.
130. Zuber TJ. Skin biopsy techniques: When and how to perform shave and excisional biopsy. *Consultant.* 2012;52(7):522-526.
131. Abdel Gabbar F, Aboulazm SF. Comparative study on gingival retraction using mechanochemical procedure and pulsed Nd = YAG laser irradiation. *Egypt Dent J.* 1995;41(1):1001-1006.
132. Acar Ö. A clinical comparison of cordless and conventional displacement systems regarding clinical performance and impression quality. *J Prosthet Dent.* 2014;111(5):388-394.

133. Al Hamad KQ, Azar WZ, Alwaeli HA, Said KN. A clinical study on the effects of cordless and conventional retraction techniques on the gingival and periodontal health. *J Clin Periodontol*. 2008;35(12):1053-1058.
134. Amirhoushang E, Mostafa M, Maryam A, Pardis N, Pedram N. Topical 0.03% atropine vs. 15% aluminum chloride in treating multiple eccrine hidrocystomas: A randomized single blind controlled study. *Indian J Dermatol*. 2010;55(1):47-49.
135. Bangha E, Elsner P. Skin problems in sugar artists. *Br J Dermatol*. 1996;135(5):772-774.
136. Baumgartner FJ, Bertin S, Konecny J. Superiority of Thoracoscopic Sympathectomy over Medical Management for the Palmoplantar Subset of Severe Hyperhidrosis. *Ann Vasc Surg*. 2009;23(1):1-7.
137. Benohanian A, Dansereau A, Bolduc C, Bloom E. Localized hyperhidrosis treated with aluminum chloride in a salicylic acid gel base. *Int J Dermatol*. 1998;37(9):701-703.
138. Brandrup F, Larsen PO. Axillary hyperhidrosis: local treatment with aluminum chloride hexahydrate 25% in absolute ethanol. *Acta Derm Venereol*. 1978;58(5):461-465.
139. Einarsdottir ER, Lang NP, Aspelund T, Pjetursson BE. A multicenter randomized, controlled clinical trial comparing the use of displacement cords, an aluminum chloride paste, and a combination of paste and cords for tissue displacement. *J Prosthet Dent*. 2018;119(1):82-88.
140. Ellis H, Scurr JH. Axillary hyperhidrosis - topical treatment with aluminium chloride hexahydrate. *Postgrad Med J*. 1979;55(654):868-869.
141. Flanagan KH, Glaser DA. An open-label trial of the efficacy of 15% aluminum chloride in 2% salicylic acid gel base in the treatment of moderate-to-severe primary axillary hyperhidrosis. *J Drugs Dermatol JDD*. 2009;8(5):477-480.
142. Flanagan KH, King R, Glaser DA. Botulinum toxin type a versus topical 20% aluminum chloride for the treatment of moderate to severe primary focal axillary hyperhidrosis. *J Drugs Dermatol JDD*. 2008;7(3):221-227.
143. Glent-Madsen L, Dahl JC. Axillary hyperhidrosis. Local treatment with aluminium-chloride hexahydrate 25% in absolute ethanol with and without supplementary treatment with triethanolamine. *Acta Derm Venereol*. 1988;68(1):87-89.
144. Gloor M, Haus J. Aluminum chloride: Is it useful for skin protection in occupational dermatology? *Exogenous Dermatology*. 2003;2(1):28-32.
145. Goh CL. Aluminium chloride hexahydrate versus palmar hyperhidrosis. Evaporimeter assessment. *Int J Dermatol*. 1990;29(5):368-370.
146. Helou J, Habre M, Soutou B, Maatouk I, Ibrahim T, Tomb R. Reversibility of hyperhidrosis post axillary depilatory laser. *Lasers Med Sci*. 2014;29(2):717-721.
147. Hjorth N, Storm D, Dela K. Topical anhydrous aluminum chloride formulation in the treatment of acne vulgaris: A double-blind study. *Cutis*. 1985;35(5):499-500.
148. Hurley HJ, Shelley WB. Special topical approach to the treatment of acne. Suppression of sweating with aluminum chloride in an anhydrous formulation. *Cutis*. 1978;22(6):696-703.
149. Jensen O. 'Rusters'. The corrosive action of palmar sweat: I. Sodium chloride in sweat. *Acta Derm Venereol*. 1979;59(2):135-138.

150. Jensen O, Karlsmark T. Palmoplantar hyperhidrosis. Treatment with alcohol solution of aluminium chloride hexahydrate: a simple method of transpiration measurement. *Dermatologica*. 1980;161(2):133-135.
151. Kalantari KK, Zeinalzade A, Kobarfard F, Moghadam SN. The effect and persistency of 1% aluminum chloride hexahydrate Iontophoresis in the treatment of primary palmar hyperhidrosis. *Iran J Pharm Res*. 2011;10(3):641-645.
152. Knapik JJ, Reynolds K, Barson J. Influence of an antiperspirant on foot blister incidence during cross- country hiking. *J Am Acad Dermatol*. 1998;39(2 1):202-206.
153. Leyden JJ, Kligman AM. Aluminum chloride in the treatment of symptomatic athlete's foot. *Arch Dermatol*. 1975;111(8):1004-1010.
154. MacFarlane IA, Knass D, Beardwell CG, Shalet SM. Hyperhidrosis in acromegaly: Effectiveness of topical aluminium chloride hexahydrate solution. *Br Med J*. 1979;2(6195):901-902.
155. Menéndez-Nieto I, Cervera-Ballester J, Maestre-Ferrín L, Blaya-Tárraga JA, Peñarrocha-Oltra D, Peñarrocha-Diago M. Hemostatic Agents in Periapical Surgery: A Randomized Study of Gauze Impregnated in Epinephrine versus Aluminum Chloride. *J Endod*. 2016;42(11):1583-1587.
156. Peñarrocha-Diago M, Maestre-Ferrín L, Peñarrocha-Oltra D, Gay-Escoda C, von-Arx T, Peñarrocha-Diago M. Pain and swelling after periapical surgery related to the hemostatic agent used: anesthetic solution with vasoconstrictor or aluminum chloride. *Med Oral Patol Oral Cir Bucal*. 2012;17(4):e594-600.
157. Peñarrocha-Diago M, Maestre-Ferrín L, Peñarrocha-Oltra D, von Arx T, Peñarrocha-Diago M. Influence of hemostatic agents upon the outcome of periapical surgery: dressings with anesthetic and vasoconstrictor or aluminum chloride. *Med Oral Patol Oral Cir Bucal*. 2013;18(2):e272-278.
158. Perdakis P, Hansen DA. An effective local application for axillary hyperhidrosis. *S Afr J Surg*. 1983;21(1):17-18.
159. Prasanna GSR, Reddy K, Kumar RKN, Shivaprakash S. Evaluation of efficacy of different gingival displacement materials on gingival sulcus width. *J Contemp Dent Pract*. 2013;14(2):217-221.
160. Quatralé RP, Thomas EL, Birnbaum JE. The site of antiperspirant action by aluminum salts in the eccrine sweat glands of the axilla. *J Soc Cosmet Chem Jpn*. 1985;36(6):435-440.
161. Quatralé RP, Waldman AH, Rogers JG, Felger CB. The mechanism of antiperspirant action by aluminium salts. I. The effect of cellophane tape stripping on aluminium salt-inhibited eccrine sweat glands. *J Soc Cosmet Chem Jpn*. 1981;32(2):67-73.
162. Rajagopal R, Mallya NB. Comparative evaluation of botulinum toxin versus iontophoresis with topical aluminium chloride hexahydrate in treatment of palmar hyperhidrosis. *Med J Armed Forces India*. 2014;70(3):247-252.
163. Rayner CR, Ritchie ID, Stark GP. Axillary hyperhidrosis, 20% aluminum chloride hexahydrate, and surgery. *Br Med J*. 1980;280(6224):1168.
164. Sáiz-Sapena N, Vanaclocha V, Panta F, Kadri C, Torres W. Operative monitoring of hand and axillary temperature during endoscopic superior thoracic sympathectomy for the treatment of palmar hyperhidrosis. *Eur J Surg*. 2000;166(1):65-69.

165. Scholes KT, Crow KD, Ellis JP, Harman RR, Saihan EM. Axillary hyperhidrosis treated with alcoholic solution of aluminium chloride hexahydrate. *Br Med J.* 1978;2(6130):84-85.
166. Shelley WB, Hurley HJ. Anhydrous formulation of aluminum chloride for chronic folliculitis. *JAMA.*244(17):1956-1957.
167. Shelley WB, Hurley HJ. Studies on topical antiperspirant control of axillary hyperhidrosis. *Acta Derm Venereol.* 1975;55(4):241-260.
168. Shen JL, Lin GS, Li WM. A new strategy of iontophoresis for hyperhidrosis. *J Am Acad Dermatol.* 1990;22(2 I):239-241.
169. Streker M, Reuther T, Hagen L, Kerscher M. Hyperhidrosis plantaris - A randomized, half-side trial for efficacy and safety of an antiperspirant containing different concentrations of aluminium chloride. *JDDG - J Ger Soc Dermatol.* 2012;10(2):115-120.
170. Stuffken M, Vahidi F. Preimpression troughing with the diode laser: A preliminary study. *J Prosthet Dent.* 2016;115(4):441-446.
171. Swary JH, West DP, Kakar R, et al. Quantitative comparison of topical aluminum salt solution efficacy for management of sweating: a randomized, controlled trial. *J Cosmet Dermatol.* 2015;14(4):E1-6.
172. Vanaclocha V, Sáiz-Sapena N, Panta F. Uniportal endoscopic superior thoracic sympathectomy. *Neurosurgery.* 2000;46(4):924-928.
173. Xhaufnaire-Uhoda E, Mayeux G, Quatresooz P, Scheen A, Piérard GE. Facing up to the imperceptible perspiration. Modulatory influences by diabetic neuropathy, physical exercise and antiperspirant. *Skin Res Technol.* 2011;17(4):487-493.
174. Yanagishita T, Tamada Y, Ohshima Y, Ito K, Akita Y, Watanabe D. Histological localization of aluminum in topical aluminum chloride treatment for palmar hyperhidrosis. *J Dermatol Sci.* 2012;67(1):69-71.
175. Zhu G, Lin JC, Kim SB, et al. Asian expert recommendation on management of skin and mucosal effects of radiation, with or without the addition of cetuximab or chemotherapy, in treatment of head and neck squamous cell carcinoma. *BMC Cancer.* 2016;16(1).
176. Monti M, Motta S. Clinical management of cutaneous toxicity of anti-EGFR agents. *Int J Biol Markers.* 2007;22(1 SUPPL. 4):S53-S61.
177. Peña-Romero AG, Toussaint-Caire S, Charli-Joseph Y, Barreda-Becerril FD, Domínguez-Cherit J. From classical to unusual: Report on 5 cases of transient reactive aquagenic pseudokeratoderma and review of the literature. *Am J Dermatopathol.* 2017;39(12):935-942.

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 **aluminum chloride hexahydrate**. 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: Aluminum chloride hexahydrate

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **aluminum chloride hexahydrate**? 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 aluminum chloride hexahydrate? Please check all th... != Compounded drug product

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

Display This Question:

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

Q2. Please list any conditions or diseases for which you use compounded **aluminum chloride hexahydrate** 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 **aluminum chloride hexahydrate** 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 aluminum chloride hexahydrate as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

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

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

- Aluminum chloride hexahydrate 20% / Hydrocortisone
- Other (please describe) _____

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

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

Q7. Over the past 5 years, has the frequency in which you have used compounded **aluminum chloride hexahydrate** 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 **aluminum chloride hexahydrate** instead of any FDA-approved drug product?

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

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

End of Block: Aluminum chloride hexahydrate

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
