Summary Report

Diphenhydramine hydrochloride

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of diphenhydramine hydrochloride (diphenhydramine HCl; UNII code: TC2D6JAD40) which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how diphenhydramine HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how diphenhydramine HCl has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of diphenhydramine HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Diphenhydramine HCl was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc for histamine-mediated reactions via capsules, gels, creams, ointments, suspensions, and solutions through the oral, mucosal, and/or topical routes of administration (ROA).

The nominator did not provide references from published peer-reviewed literature to describe the pharmacology and support the clinical use of diphenhydramine HCl.

The reason provided for nomination to the 503B Bulks List is intolerances or allergies to inactive ingredients, or commercially available dosage forms are not appropriate for specific patient needs, such as use of tablets or injection solutions for compounding transdermal preparations.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of diphenhydramine HCl 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, 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 diphenhydramine HCl; name variations of diphenhydramine HCl 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 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing diphenhydramine HCl. 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

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: diphenhydramine HCl and topical or mucosal administration (refer to Appendix 1 for full search strategies). Terms for oral administration were not included in the search strategies due to availability of FDA-approved oral products. Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 24, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on March 24, 2020 for clinical practice guidelines that recommended the use of diphenhydramine HCl and provided sufficient information on dosing and administration. A systematic literature review was not performed for oral administration because FDA-approved diphenhydramine HCl products are available for administration via this route.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which diphenhydramine HCl was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if diphenhydramine HCl was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which diphenhydramine HCl was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of diphenhydramine HCl; setting; total number of patients; number of patients who received diphenhydramine HCl; patient population; indication for use of diphenhydramine HCl; dosage form and strength; dose; ROA; frequency and

duration of therapy; use of diphenhydramine HCl in a combination product; use and formulation of diphenhydramine HCl in a compounded product; use of diphenhydramine HCl compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances diphenhydramine HCl was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use diphenhydramine HCl: allergy and immunology, dermatology, and primary care and internal medicine. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of diphenhydramine HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched 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 email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1, were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Diphenhydramine HCl is available as an FDA-approved product in the nominated dosage form and ROA.
- Diphenhydramine HCl is available in various oral and topical dosage forms as OTC products in the US.
- There is a current United States Pharmacopeia (USP) monograph for diphenhydramine HCl.
- Diphenhydramine HCl is available in the nominated dosage form and ROA in Hong Kong, Namibia, New Zealand, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Diphenhydramine HCl	25-50 mg	Capsule	Oral	Prescription	7/1/2009
	12.5 mg/5 mL	Elixir, solution			2/10/1982

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Diphenhydramine HCl	2%	Cream	Topical	UK	Pharmacy-only[c]	12/4/1989
	25-50 mg	Capsule	Oral	Hong Kong	Pharmacy-only[c]	3/31/1979
				Namibia	–	12/22/1981
				New Zealand	Restricted	7/2/1997
	2 mg/mL	Solution		Hong Kong	Pharmacy-only[c]	6/27/2000

Abbreviation: "– ", not mentioned.

[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.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 632 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 495 titles and abstracts were screened. After screening, the full text of 125 articles was reviewed. Finally, 9 studies were included. One hundred sixteen studies were excluded for the following reasons: diphenhydramine HCl only mentioned briefly (51 studies); wrong study design (30); FDA-approved formulation (17); diphenhydramine HCl used as brand or proprietary product (7); wrong dosage form or ROA (5); duplicate study (2); diphenhydramine HCl not used clinically (2); wrong substance (2).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 9 included studies were published between 1947 and 2019. There were 4 experimental studies, 1 observational study, 6 descriptive studies, and 0 clinical practice guidelines. The 9 studies were all conducted in the US.

A total of 561 patients participated in the 9 included studies. The number of patients in each study ranged from 1 to 268.

Outcome measures differed among the included studies and included: resolution/control of pruritus, lesions, and/or rashes; patient reported relief of itching; and itch intensity and duration.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of diphenhydramine HCl

Five hundred forty-one patients received diphenhydramine HCl as a treatment for pruritis, administered topically as a 2-5% ointment or lotion. Duration of treatment ranged from once to 2 months.

Refer to Table 6 for the summary of dosage by indication.

Diphenhydramine HCl was used as a compounded product (refer to Table 9).

In 1 study, the authors' concluding statement noted that the patient had a partial response to topical and oral diphenhydramine for treatment of urticaria-like follicular mucinosis.[6] In another study, the author concluded that it is worthwhile to give a trial of diphenhydramine ointment in all cases of pruritic dermatoses with an allergic or neurogenic background,[7] while another author stated diphenhydramine ointment was indicated for control of various itching dermatoses.[8] In 2 studies, the authors' concluding statement noted a portion of the patients had relief from itching with diphenhydramine ointment.[9,10] In 2 studies, the authors' concluding statement had an experimental treatment that was superior to that of diphenhydramine for pruritus.[11,12] In 2 studies, the authors' concluding statement was not specific to diphenhydramine.[13,14] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

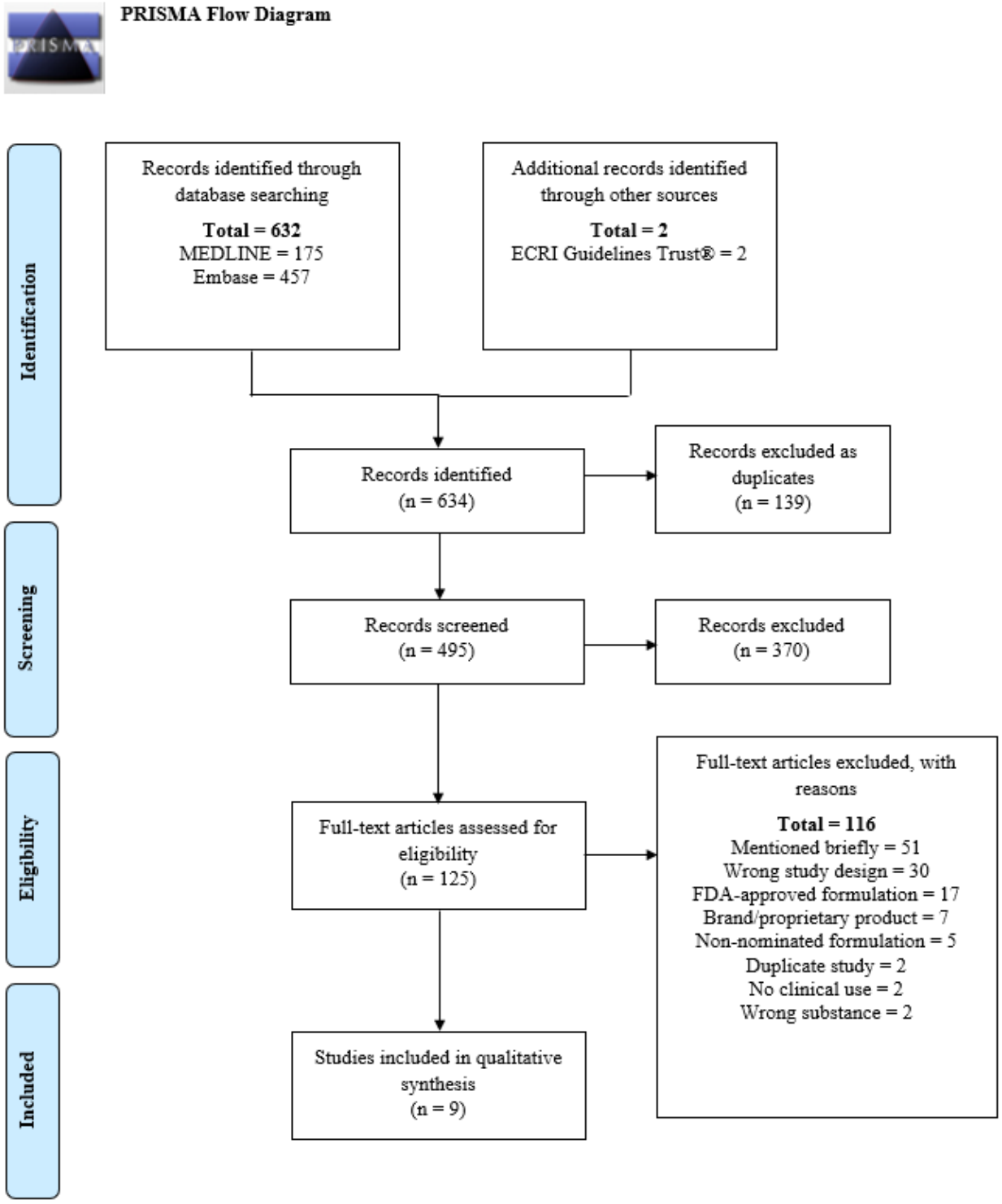
In addition to the 9 included studies, 8 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of diphenhydramine HCl.

Diphenhydramine is a first-generation antihistamine with oral FDA-approved products; various oral and topical OTC products are also available. Several studies have investigated the topical route for diphenhydramine, which are summarized in the literature review section. Two studies mentioned why they chose to explore the topical route. One study from 1949 noted that the frequency of side effects from diphenhydramine taken orally led them to investigate diphenhydramine's topical use for diseases with cutaneous manifestations of an allergic nature.[9] Another study from 1946 noted that local application of diphenhydramine reduced the wheal reaction produced by application of histamine to the skin and suggested that local application should be more effective than oral administration in inhibiting histamine wheals.[15]

Topical diphenhydramine can cause systemic toxicity when applied in patients with varicella-zoster infections and possibly other skin disorders that cause extensive disruption of the skin barrier.[16] There have been reports of diphenhydramine toxicity in young children with chicken pox as well as in an adult with eczema.[16,17] Using topical diphenhydramine in children with chicken pox can cause systemic absorption and severe toxicity because the skin barrier is disrupted and the nature of the condition requires repeated application to large areas of the body.[17] Because diphenhydramine is an antihistamine with anticholinergic properties, manifestations of toxicity include dilated pupils, flushed face, dry mouth, confusion, paradoxical hyperactivity, disorientation, hallucinations, and ataxia.[17] Diphenhydramine can also cause allergic contact dermatitis.[18,19] Once a patient develops sensitization to a topical antihistamine, systemic administration of that antihistamine or any other antihistamine in the same class will cause systemic contact dermatitis.[18,20] Due to numerous reports of contact dermatitis from topical OTC and prescription drugs, the FDA has drafted rules for topical drugs with diphenhydramine.[21] In the past, antihistamines were widely included in topical medications to relieve itching,[19] the most popular being diphenhydramine even though it caused allergic contact dermatitis. Over time, antihistamines have largely been replaced by corticosteroids in topical products.[19] A 2015 study discussed that the current antihistamines, which help with treating itch of allergic causes, are mostly ineffective in controlling itch associated with diseases like atopic eczema or psoriasis.[11]

In a 1990 article written about therapeutic recommendations for aphthous ulcerations in children, the author mentions Benylin® and Benadryl® (diphenhydramine in alcohol), an available OTC topical anesthetic.[22] The Benylin® elixir was less irritating than Benadryl because it had a lesser alcohol concentration and selective anesthetization of ulcers.[22]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	Number of Studies
Descriptive[6,7,9,10,13,14]	6
Experimental[9-12]	4
Observational[8]	1

[a]Studies 9 and 10 were counted as both descriptive and experimental.

Table 4. Number of studies by country

Country	Number of Studies
US[6-14]	9
	Total US: 9 Total Non-US Countries: 0

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Callen *et al*, 1981, US[14]	–	15 patients with pruritic urticarial papules and plaques of pregnancy (PUPPP) (0%, range 19-35 y)	• Topical corticosteroids (3) • Topical corticosteroids, diphenhydramine* (8) • Topical corticosteroids, diphenhydramine, hydroxyzine, prednisone (1) • Topical corticosteroids, diphenhydramine, hydroxyzine (1) • Lubricants only (1) • None (1) *Route of administration for diphenhydramine not specified	Control of pruritus, resolution of lesions	Recognizing and distinguishing PUPPP from popular dermatitis and herpes gestation is important because mild symptomatic therapy can usually be substituted for systemic corticosteroids.
Harvey *et al*, 2019, US[6]	Case report	1 patient with urticaria-like follicular mucinosis (0%, 37 y)	No comparator; used oral steroids, topical and oral diphenhydramine	Resolution of pruritus and rash	Patient had partial response to oral steroids, topical and oral diphenhydramine. Treatment response for urticaria-like follicular mucinosis is variable.
McGavack *et al*, 1948, US[9]	–	74 patients with various itching dermatoses (gender and age not specified)	• Ointment 1 with 5% diphenhydramine (56) • Ointment 2 with 2% diphenhydramine (18) • Ointment base as control was applied whenever possible to another area of the body (number of patients not specified)	Effect of ointment on itching and progress of underlying lesion (complete relief, improvement, no relief)	Out of 74 patients, 44 patients had complete relief from the itching and 18 patients had improvement. There were 6 patients who had some discomfort from the application of the ointment especially when the 5% one was used. No systemic side reactions were observed.
Napatalung *et al*, 2015, US[13]	Case report	1 patient (100%, 77 y)	No comparator; used oral cetirizine, topical diphenhydramine, and topical zinc oxide paste	Control of pruritus	"Intertriginous cutaneous mastocytosis is a rare disorder, and clinicopathologic correlation was essential in successfully interpreting this unusual presentation."

Orecklin, 1949, US[7]	Series	268 patients with various pruritic dermatoses (gender and age not provided)	• Diphenhydramine HCl ointment (268)	Patient reported relief of itching	Diphenhydramine HCl ointment is purely palliative and has no effect on the progression of dermatoses except pruritus relief. It is worth to give a trial of diphenhydramine HCl ointment in all cases of pruritic dermatoses that have either an allergic or neurogenic background.
Papoiu *et al*, 2013, US[12]	Double-blinded, vehicle-controlled crossover study	32 healthy subjects (44%, range 21-58 y)	• Diphenhydramine (32) • Hydrocortisone (32) • Strontium chloride hexahydrate (32) • Control vehicle (32)	Itch intensity on a numerical visual analog scale and the duration	The 4% topical strontium formulation had a robust antipruritic effect for histamine-mediated itches as well as for non-histaminergic pruritus induced via the proteinase activated receptors 2 pathway via cowhage.
Papoiu *et al*, 2015, US[11]	Double-blinded, vehicle-controlled, randomized, crossover study	48 healthy subjects (42%, range 19-50 y)	• Diphenhydramine (48) • Hydrocortisone (48) • TriCalm hydrogel contains active ingredient aluminum acetate (48) • Hydrogel vehicle as control (48)	Itch intensity on a numerical visual analog scale and the duration	The TriCalm hydrogel was superior to the other 2 tested treatments in reducing peak itch intensity, total itch perceived, and itch duration. From antipruritic action, TriCalm hydrogel was 8 times more effective than hydrocortisone and almost 6 times more effective than diphenhydramine.
Perry, 1947, US[10]	–	22 patients with a variety of dermatoses (gender and age not provided)	• Diphenhydramine ointment (22) • Ointment base alone* (8) *Eight patients out of the 22 who received diphenhydramine ointment were given ointment base alone if they showed antipruritic effects	Relief of pruritis (none, slight, moderate, or excellent)	Six out of 22 patients had moderate relief of itching and 2 had excellent relief. Of those 8 cases, 4 had the same antipruritic effect with the ointment base alone.
Philip, 1949, US[8]	Case control	100 patients with itching dermatoses (41%, range 0.5-72 y)	• Diphenhydramine (85) • Control (15)	Patient reported relief of itching	Diphenhydramine ointment has indications for control of various itching dermatoses, especially where an allergic-like histamine liberation plays a major role.

Abbreviations: "–", not mentioned; PUPPP, pruritic urticarial papules and plaques of pregnancy.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pruritis[6-14]	–	–	–	–	–
	0.8 mL	2-5%	Lotion, ointment	Topical	Once – 2 months

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No included studies from non-US countries

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Pruritis[10-12]	1947-2015	Not mentioned, reports receiving diphenhydramine from LaVita Compounding Pharmacy in San Diego, CA[11,12]	Lotion, ointment	2%
		Benadryl in a base containing cetyl alcohol, carbowax 1,000 monosterate, methyl p-hydroxyl benzoate, and water[10]		

Table 10. Compounded products – non-US countries

No included studies from non-US countries

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Seven SMEs discussed diphenhydramine HCl. The 7 SMEs were medical doctors. The SMEs specialized and/or were board-certified in allergy and immunology, dermatology, family medicine, and pulmonology, working in academic medical centers and hospital/health systems. The SMEs had been in practice for 14 to 34 years.

Several SMEs stated that topical diphenhydramine, which can be mixed with steroids and/or a moisturizer to help soothe inflammatory skin conditions, has mostly been used for pruritus or poison ivy. However, a few SMEs stated that while topical diphenhydramine would treat itching, it does not treat the underlying condition that is causing the itching. A topical steroid or immune modulator is more commonly used because it is more effective at treating the underlying condition. One exception to this is putting topical diphenhydramine on mucus membranes which provides an anesthetic effect. This can be used in patients who have bad oral mucosal diseases such as Behcet's, gingivitis, or gingival ulcers. Topical diphenhydramine is administered orally that the patient swishes and spits; it can also be mixed with Maalox. Other SMEs mentioned diphenhydramine as part of a "magic mouthwash" for oral sores along with other drugs, such as lidocaine to numb, and sometimes an antibiotic for patients with painful strep throat, to gargle.

The SMEs had different views on the nominated formulations. One SME was indifferent to having more formulations available but stated that there is a known sensitization with topical diphenhydramine. This SME stated an old formulation of Caladryl®, which had calamine with topical diphenhydramine, as an example of something dermatologists did not like to use because it could be sensitizing when used topically. Patients with atopic dermatitis also have a higher rate of developing contact dermatitis. Another SME did not typically use topical diphenhydramine. If a patient was allergic to an excipient in the commercially available product, then the SME would look for a different product or treatment method. This SME also commented that liquids could be helpful as adjunctive therapy since they are faster acting. One SME used diphenhydramine frequently in any formulation available, including creams, injectables, and oral products and commented that the availability of gels would be nice. Another SME frequently used diphenhydramine orally and as a solution because this SME saw a lot of patients with itching. If there is a need for a higher dose, then the SME increased the number of tablets or capsules. This SME had not prescribed diphenhydramine via the mucosal or topical routes. Another SME stated that there are people doing interesting things, especially in the emergency room so maybe diphenhydramine via those routes are used as part of a gastrointestinal cocktail for mouth ulcers. There is some use of a "swish and swallow or slurry for topical Benadryl." The SME thought it was interesting that the nominated indication was for histamine-mediated reactions because while this SME had treated people with swelling in the tongue, throat, and lips, only oral or intravenous (IV) was used in patients with these signs. This SME did not think there would be a benefit for topical over IV when dealing with an acute, emergent condition.

While diphenhydramine was not nominated as an injection, one SME did comment that in the emergency room and the intensive care unit, diphenhydramine IV or intramuscular (IM) is used and is effective. Another SME stated that if someone comes in with an acute allergic reaction, IM diphenhydramine might be given.

Results of survey

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

The survey respondent used diphenhydramine HCl, but not as a topical ointment.

The survey respondent did not use diphenhydramine HCl for histamine-mediated reactions and did not list any other uses. No response was given to the question regarding indications.

The survey respondent did not respond to questions about why compounded diphenhydramine HCl was used, stocking non-patient specific diphenhydramine HCl, or how compounded diphenhydramine HCl was obtained.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Response, n (N=1)**
Doctor of Medicine (MD)	1
Practice Setting	**Response, n (N=1)**
Physician office or private practice	1

Table 12. Conditions for which diphenhydramine HCl prescribed or administered

Condition	**Response, n (N=1)[a]**
Histamine-mediated reactions	0
No Response	1

[a]Out of 1 respondent, 1 reported prescribing or using diphenhydramine HCl.

Table 13. Reasons for using compounded diphenhydramine HCl

Reason	**Response, n (N=1)[a]**
Commercial product not available in desired dosage form, strength or combination	0
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	0
No commercial products	0
No response	1

[a]Out of 1 respondent, 1 reported prescribing or using diphenhydramine HCl.

Table 14. Use of non-patient-specific compounded diphenhydramine HCl

Do you stock non-patient-specific compounded diphenhydramine HCl at your practice?	**Response, n (N=1)**
Yes	0
No	0
No response	1
How do you obtain your stock of non-patient-specific compounded diphenhydramine HCl?	**Response, n (N=1)**
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	0
Purchase from outsourcing facility	0
No response	1

CONCLUSION

Diphenhydramine HCl was nominated for inclusion on the 503B Bulks List for histamine-mediated reactions via capsules, gels, creams, ointments, suspensions, and solutions through oral, mucosal and/or topical ROAs. Diphenhydramine HCl is available as FDA-approved products as oral capsules, elixirs, and solutions and in various oral and topical dosage forms as OTC products in the US. Diphenhydramine HCl is also available in the nominated dosage form and ROA in Hong Kong, Namibia, New Zealand, and UK.

From the literature review and interviews conducted, topical diphenhydramine is used frequently for pruritus. Diphenhydramine can also be part of a "magic mouthwash" for oral sores along with other drugs such as lidocaine as an anesthetic, and sometimes with an antibiotic for patients with painful strep throat as a gargle. There have been reports of topical diphenhydramine causing systemic toxicities in certain patient populations and allergic contact dermatitis. Of the 9 studies included for the literature review, 5 studies specified that they administered diphenhydramine topically as an ointment or lotion.

The SMEs had different views regarding the nominated formulations. One was indifferent to having more formulations available. Another rarely used topical diphenhydramine but thinks liquids could be helpful as adjunctive therapy. A third used the available diphenhydramine formulations frequently and thought the availability of gels would be beneficial. The last SME did not use diphenhydramine via the mucosal or topical routes but frequently uses diphenhydramine orally.

From the survey responses, the one respondent used diphenhydramine HCl, but did not indicate that compounded diphenhydramine HCl was used, and did not provide responses about the dosage form, ROA, indications, reasons for use, or stocking practices.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 23, 2020
- Date last searched: March 24, 2020
- Limits: Humans (search hedge); English language
- Number of results: 175

1	diphenhydramine/	3922
2	difenh#dramin$.tw.	4
3	diphenh#drami#$.tw.	3562
4	diphenylh#dramin$.tw.	31
5	or/1-4	5778
6	administration, topical/	38078
7	administration, cutaneous/	21804
8	administration, mucosal/	251
9	topical$.tw.	103077
10	percutaneous$.tw.	141643
11	transdermal$.tw.	14278
12	mucosal$.tw.	118072
13	gels/	28601
14	suspensions/	7697
15	liniments/	122
16	ointments/	12746
17	skin cream/	983
18	suspension?.tw.	106942
19	gel?.tw.	304164
20	liniment?.tw.	143

21	ointment?.tw.	11661
22	salve?.tw.	338
23	paste?.tw.	12162
24	unguent$.tw.	111
25	lotion?.tw.	2265
26	cream?.tw.	18521
27	or/6-26	828894
28	and/5,27	296
29	exp animals/ not humans/	4681428
30	28 not 29	195
31	limit 30 to english language	175

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 24, 2020
- Limits: Humans (search hedge); English language
- Number of results: 457

1	diphenhydramine'/mj	6937
2	difenhidramin*':ti,ab,tn	4
3	difenhydramin*':ti,ab,tn	5
4	diphenhidramid*':ti,ab,tn	0
5	diphenhydramid*':ti,ab,tn	1
6	diphenhidramin*':ti,ab,tn	4
7	diphenhydramin*':ti,ab,tn	5628
8	diphenylhydramin*':ti,ab,tn	66
9	diphenylhidramin*':ti,ab,tn	0
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	10420
11	topical drug administration'/de	81536
12	cutaneous drug administration'/de	618
13	mucosal drug administration'/de	416
14	transdermal drug administration'/de	8883
15	topical*':ti,ab	146272
16	percutaneous*':ti,ab	216395
17	transdermal*':ti,ab	20815
18	mucosal*':ti,ab	167917
19	cream'/de	9180
20	gel'/exp	73480
21	liniment'/de	248
22	lotion'/de	2804

23	ointment'/exp	18376
24	paste'/de	2490
25	salve'/de	165
26	suspension'/exp	108612
27	cream$':ti,ab	29020
28	liniment$':ti,ab	231
29	lotion$':ti,ab	3941
30	ointment$':ti,ab	21285
31	paste$':ti,ab	14635
32	salve$':ti,ab	469
33	suspension$':ti,ab	142437
34	unguent*':ti,ab	239
35	gel$':ti,ab	357380
36	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	1229490
37	#10 AND #36	689
38	[animals]/lim NOT [humans]/lim	6007063
39	#37 NOT #38	509
40	#37 NOT #38 AND [english]/lim	457

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded diphenhydramine hydrochloride. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this 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.

Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

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.

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

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer diphenhydramine hydrochloride to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer diphenhydramine hydrochloride by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Topical ointment
   - o None of the above

4. I prescribe or administer diphenhydramine hydrochloride for the following conditions or diseases: (check all that apply)

   - o Histamine-mediated reactions
   - o Other (please explain) _____

5. I use compounded diphenhydramine hydrochloride because: (check all that apply)

   - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
   - o Patient allergies prevent me from using commercially available products. (please explain)_____
   - o Patient conditions prevent me from using commercially available products. (please explain) _____
   - o There are no commercially available products containing diphenhydramine hydrochloride.
   - o Other (please explain) _____

6. Do you stock non-patient-specific compounded diphenhydramine hydrochloride at your practice?

   - o Yes
   - o No
   - o I'm not sure

7. I obtain compounded diphenhydramine hydrochloride from the following: (check all that apply)

   - o Compound myself at my practice
   - o Have the product compounded by an in-house pharmacy
   - o Purchase, or have a patient purchase, from a compounding pharmacy
   - o Purchase, or have a patient purchase, from an outsourcing facility
   - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

   - o Physician office/private practice
   - o Outpatient clinic
   - o Hospital/health system
   - o Academic medical center
   - o Emergency room
   - o Operating room
   - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

   - o Doctor of Medicine (MD)
   - o Doctor of Osteopathic Medicine (DO)
   - o Doctor of Medicine in Dentistry (DMD/DDS)
   - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
   - o Naturopathic Doctor (ND)
   - o Nurse Practitioner (NP)
   - o Physician Assistant (PA)
   - o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.