Summary Report

Pramoxine Hydrochloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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REVIEW OF NOMINATIONS

Pramoxine hydrochloride (pramoxine HCl; UNII code: 88AYB867L5) was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) and Sincerus Florida, LLC. While the exact medical condition is which the compounded drug is being requested may be unknown, pramoxine HCl is generally used to treat pruritus and dermatitis. Pramoxine HCl was nominated for use as a topical product in a dosage form based on the prescriber's request including a spray and scalp oil. The strength compounded will also be based on the prescriber's request with the therapeutic dose being 1%. Pramoxine HCl was also nominated for 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:

- Patients respond differently and the compounded product may be the only formulation that effectively treats the indication for which it is intended to treat.
- Patient sensitivities and allergies to inactive ingredients found in commercially available products may lead to treatment failures. Compounding from bulk ensures that only the ingredients necessary to achieve the desired clinical outcome are utilized avoiding any ingredients that may be irritating, hazardous, or allergenic.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- The commercially available product cannot be used to compound the nominated dosage forms.
- The need to compound in combination with other APIs that are not commercially available.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of pramoxine 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, 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 pramoxine HCl; name variations of pramoxine 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(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or routes of administration 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

pramoxine 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

Two databases (PubMed and Embase) were searched including any date through May 9, 2019. The search included a combination ("pramoxine hydrochloride"[TIAB] OR pramoxine[TIAB] OR pramocaine[TIAB]) AND (desoximetasone[TIAB] OR menthol[TIAB] OR tranilast[TIAB] OR "betamethasone dipropionate"[TIAB] OR "fluocinolone acetonide"[TIAB] OR olive[TIAB] OR emu[TIAB] OR "clobetasol propionate"[TIAB] OR spray OR oil OR topical) 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. Microsoft Excel® was used for screening purposes.

Study selection

Articles were not excluded on the basis of study design. Pramoxine HCl is a component of an FDA-approved product, as a result, articles were excluded if pramoxine HCl was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Articles were considered relevant based on the identification of a clinical use of pramoxine HCl or the implementation of pramoxine HCl in clinical practice. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

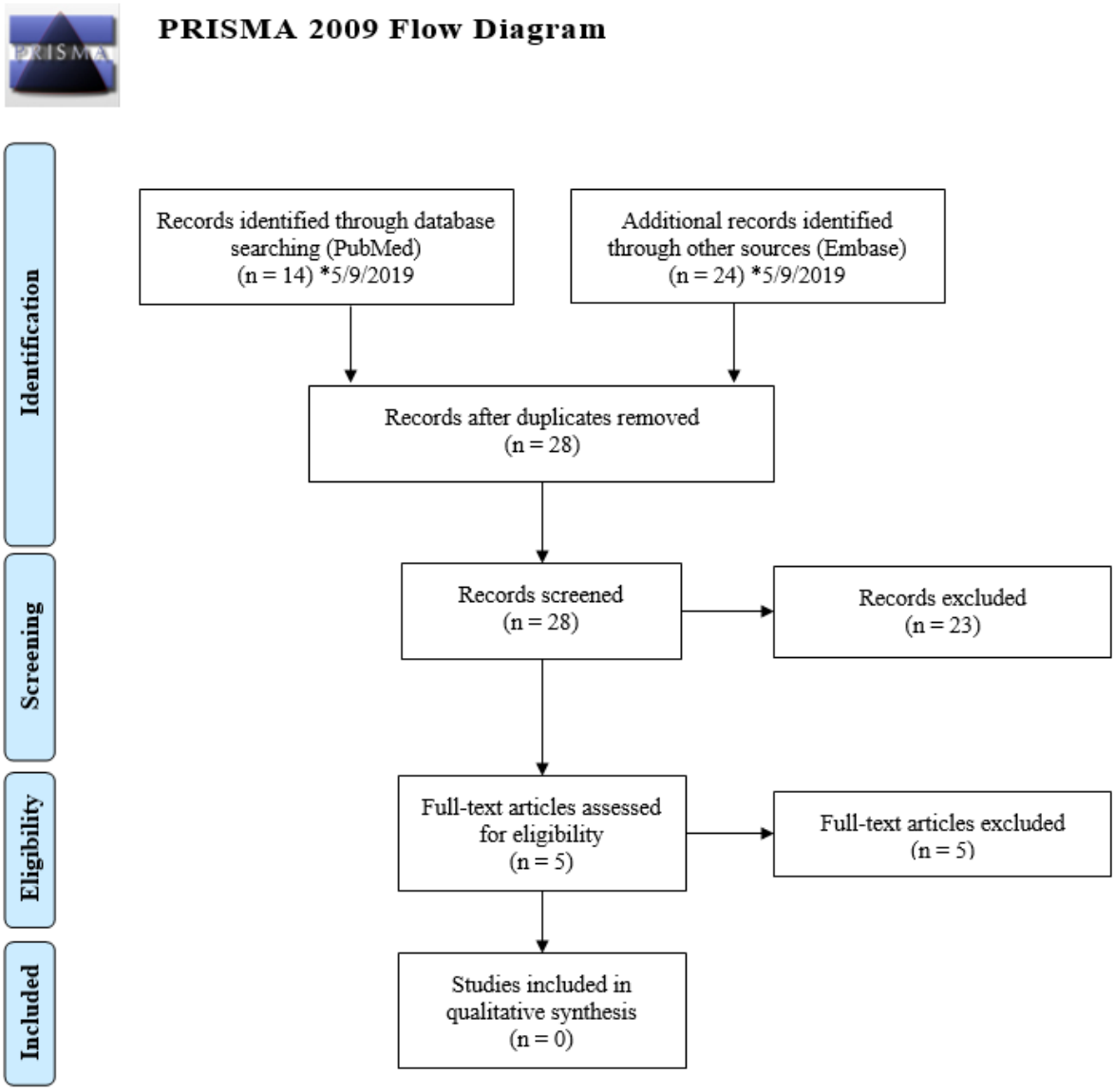
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for pramoxine HCl 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 pramoxine HCl compared to alternative therapies.

Results

Please refer to Figure 1.

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



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *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, one (1) medical specialties that would potentially use pramoxine HCl were identified: dermatology. 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 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, identified from the nominations, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to four (4) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

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

Table 1. Participating associations

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

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Pramoxine HCl is not available as an FDA-approved topical spray or scalp oil product. It is available as topical cream, lotion, and foam products.
- Pramoxine HCl is available as an OTC product in the US.
- There is a current United States Pharmacopoeia (USP) monograph for pramoxine HCl.
- Pramoxine HCl is not available in the selected non-US countries and regions as a topical spray or scalp oil. It is available as ointments, suppositories, and foam products in Abu Dhabi, Canada, Hong Kong, Ireland, and Namibia.

Table 3. Currently approved products – US

No approved products in the US

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

No approved products in the selected non-US countries and region

Summary of literature review

No studies identified that met the inclusion criteria.

Table 5. Types of studies

No studies identified that met the inclusion criteria

Table 6. Number of studies by country

No studies identified that met the inclusion criteria

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Pramoxine HCl 1% / Not mentioned[a]	0
	Pramoxine HCl 1% / Desoximetasone 0.05% / Menthol 2% / Tranilast 0.5%	0
	Pramoxine HCl 1% / Betamethasone dipropionate 0.05% / Menthol 2% / Tranilast 0.5%	0
	Pramoxine HCl 1% / Fluocinolone acetonide 0.01% – in emu and olive oil	0
	Pramoxine HCl 1% / Clobetasol propionate 0.05% - in emu and olive oil	0

[a]Nomination identified the need for combination products. However, no information was provided regarding specific combination desired.

Table 8. Dosage by indication – US

No studies identified that met the inclusion criteria

Table 9. Dosage by indication – non-US countries

No studies identified that met the inclusion criteria

Table 10. Compounded products – US

No studies identified that met the inclusion criteria

Table 11. Compounded products – non-US countries

No studies identified that met the inclusion criteria

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 Pramoxine HCl	Interview Summary Response
DER_06	MD	Dermatology Dermatology/Immunology	Independent consultant	Yes	• Used to relieve itching in combination with topical steroids • Does not see need for office stock unless being dispensed

Abbreviation: MD, Doctor of Medicine.

Use of pramoxine HCl

- The interviewee stated that it was used to relieve itch if relatively small and localized (unlike the other caine's which are used "really specifically for these pre-procedure anesthesia things").
- Said that "it is better than putting a topical antihistamine on."
    - "I have never, ever been a fan of the topical Benadryl, Saladryl family, because we worry about anesthetics and getting allergies to some of them. Same thing comes up by the way with the topical caine's, you can develop an allergy to it. Pramoxine's been out, and it's in Pramosone, which is a combo part that's a hydrocortisone. I think it's sarna, yeah S-A-R-N-A, is a product that's just plain old pramoxine. Yeah it is, Sarna is Pramoxine hydrochloride. That is relatively... It's an over the counter product. The idea of giving Pramoxine with several different topical steroids to relieve an exudative condition, whether it's atopic dermatitis, contact allergy, sort of makes sense."
- Confirmed that there is a rationale that could justify mixing pramoxine with different steroid products that are not commercially available.

Use of "office stock"

- The interviewee does not see need for office stock unless they plan to dispense it to patients or are a wholesaler. It is not for treatment in the office; it is treatment for after the patient leaves.

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 Response	0	3

Abbreviation: Abbreviations: MD, Doctor of Medicine.

Table 14. Types of products used, prescribed, or recommended[a]

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

[a]Out of four (4) respondents, one (1) reported using, prescribing, or recommending pramoxine HCl products.

Table 15. Compounded use of pramoxine HCl in practice

No survey respondents provided this information

Table 16. Indications for which pramoxine HCl is considered a standard therapy

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

CONCLUSION

Pramoxine HCl (UNII code: 88AYB867L5) was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) and Sincerus Florida, LLC. While the exact medical condition is which the compounded drug is being requested may be unknown, pramoxine HCl is generally used to treat pruritus and dermatitis. Pramoxine HCl was nominated for use as a topical product in a dosage form based on the prescriber's request including a spray and scalp oil. The strength compounded will also be based on the prescriber's request with the therapeutic dose being 1%.. Pramoxine HCl is not available as an FDA-approved product, but is available as an OTC product in the US. There is a current USP monograph for pramoxine HCl. Pramoxine HCl is not available in any of the national medical registries searched.

No studies were identified that met the inclusion criteria for the literature review.

The interviewee stated that pramoxine HCl is used to relive itching in combination with topical steroids. They did not see a need for office stock unless the intent is to dispense since it is not intended for in-office treatment.

From the survey responses, one (1) out of four (4) respondents reported using, prescribing, or recommending pramoxine HCl in practice, but did not specify the type of product used.

APPENDICES

Appendix 1. References

No studies identified that met the inclusion criteria.

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 **pramoxine**. 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: Pramoxine

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **pramoxine**? 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 pramoxine?... != Compounded drug product Is Not Selected

Skip To: Q2. If What type(s) of product(s) do you use, prescribe, or recommend for pramoxine?... = Compounded drug product Is Selected

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for pramoxine?... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **pramoxine** 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 **pramoxine** 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 pramoxine as a single agent active ingredient, or as on... != Combination Is Not Selected

Display This Question:

If Loop current: Do you use compounded pramoxine as a single agent active ingredient, or as on... = Combination Is Selected

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

- ☐ Pramoxine HCl 1% / Clobetasol propionate 0.05% in Emu and Olive oil
- ☐ Pramoxine HCl 1% / Fluocinolone acetonide 0.01% in Emu and Olive oil
- ☐ Pramoxine HCl 1% / Betamethasone dipropionate 0.05% / Menthol 2% / Tranilast 0.5%
- ☐ Pramoxine HCl 1% / Desoximetasone 0.05% / Menthol 2% / Tranilast 0.5%
- ☐ Other (please describe)_____

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

_____

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

_____

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

_____

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

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded pramoxine in your practice locat... = No

Display This Question:

If Do you stock non-patient-specific compounded pramoxine in your practice locat... = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **pramoxine**? 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 **pramoxine**? 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 **pramoxine**? 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 pramoxine? Please... = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded pramoxine? Please... = Emergencies

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

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

_____

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

_____

End of Block: Pramoxine

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) _____