Summary Report

Cyclobenzaprine 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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Prepared by:

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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 cyclobenzaprine hydrochloride (cyclobenzaprine HCl; UNII code: 0VE05JYS2P), 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 cyclobenzaprine 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 cyclobenzaprine 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 cyclobenzaprine 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

Cyclobenzaprine HCl was nominated for inclusion on the 503B Bulks List by Fagron.

Cyclobenzaprine HCl was nominated for myofascial pain via a topical 1-3% cream.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of cyclobenzaprine HCl.[6-13]

The reason provided for nomination to the 503B Bulks List was that the amount of cyclobenzaprine tablets required to compound a cream would require a large powder volume and could lead to increased risk of skin irritation due to excipients. Myofascial creams are meant to be applied to trigger points on the muscle, therefore the cream must be potent enough for small application volumes.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of cyclobenzaprine 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 cyclobenzaprine HCl; name variations of cyclobenzaprine 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 cyclobenzaprine 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: cyclobenzaprine and topical administration (refer to Appendix 1 for full search strategies). 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 April 5, 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 April 5, 2020 for clinical practice guidelines that recommended the use of cyclobenzaprine and provided sufficient information on dosing and administration.

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 cyclobenzaprine 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 cyclobenzaprine 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 cyclobenzaprine 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 cyclobenzaprine HCl; setting; total number of patients; number of patients who received cyclobenzaprine HCl; patient population; indication for use of cyclobenzaprine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of cyclobenzaprine HCl in a combination product; use and formulation of cyclobenzaprine HCl in a compounded product; use of cyclobenzaprine 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 cyclobenzaprine HCl was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use cyclobenzaprine HCl: orthopedics, pain management, and rheumatology. 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 cyclobenzaprine 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

- Cyclobenzaprine HCl is not available as an FDA-approved product in the nominated dosage form and ROA.
- Cyclobenzaprine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for cyclobenzaprine HCl.
- Cyclobenzaprine HCl is not available in the nominated dosage form and ROA in any of the national medical registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 125 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 111 titles and abstracts were screened. After screening, the full text of 26 articles was reviewed. Finally, zero studies were included. Twenty-six studies were excluded for the following reasons: wrong study design (20 studies); used in dosage form, ROA, or combination that was not nominated (5); cyclobenzaprine HCl only mentioned briefly (1).

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

Characteristics of included studies

No studies were included from the literature review.

Use of cyclobenzaprine HCl

No studies were included from the literature review.

Pharmacology and historical use

Five studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of cyclobenzaprine HCl.

In a 2016 review by Cline, the author mentioned that cyclobenzaprine HCl is “often compounded into topical analgesics (off-label use) for musculoskeletal conditions because it is highly effective in muscle tissue at the site of pain, allowing for effective dosing without the systemic adverse effect of somnolence.”[14]

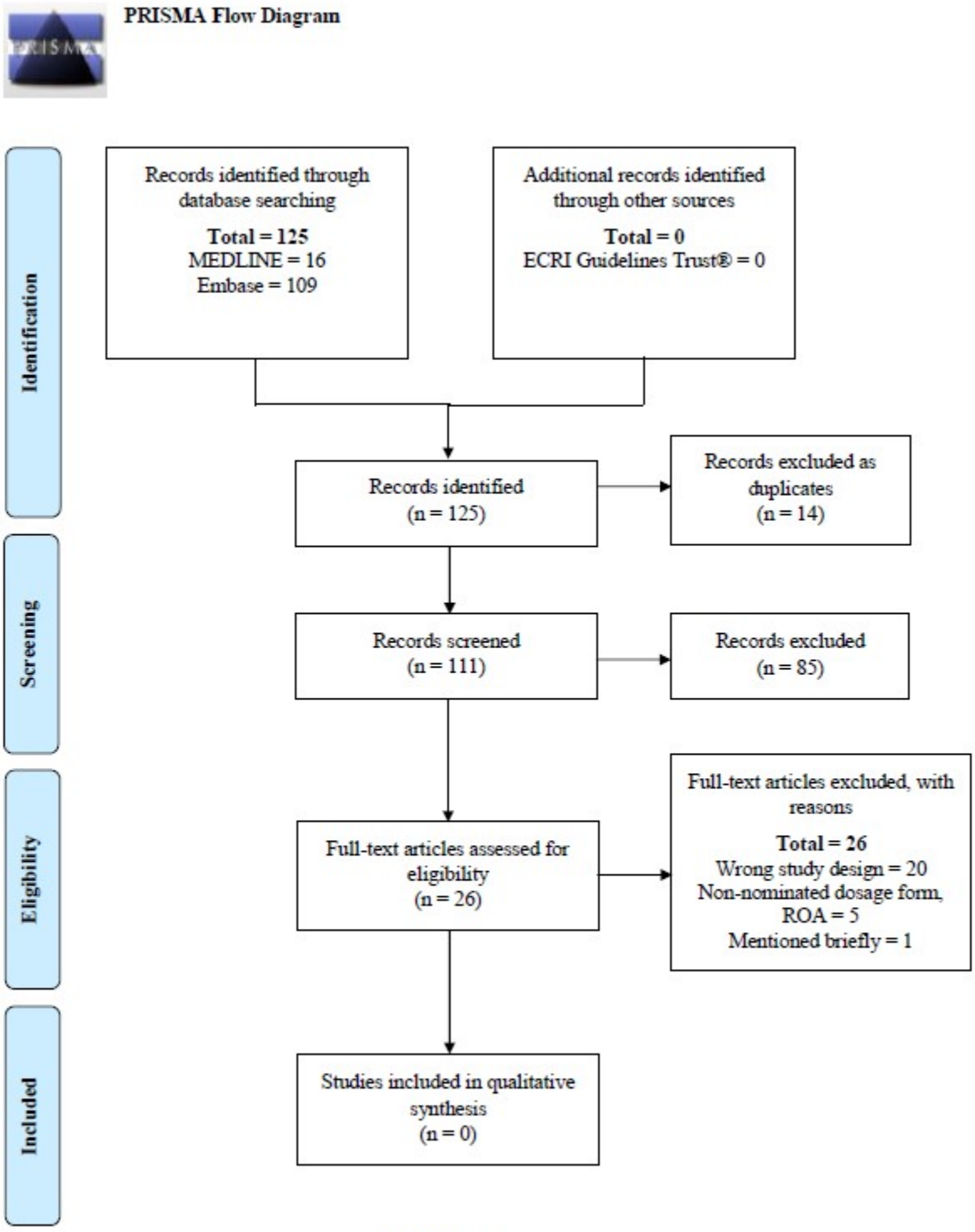
One study on the use of compounded transdermal medications for chronic pain issues listed a combination of ketoprofen 10-20%, cyclobenzaprine 1%, and bupivacaine 0.5%, to be applied 2-3 times per day as needed for low back pain and arthritis, though it did not provide details about efficacy.[15] Another article briefly mentioned a similar combination of ketoprofen 10%, cyclobenzaprine 1%, and lidocaine 5% in a poloxamer organogel formulation, to be used for patients with arthritis and sore muscles.[16] Though this article provided the formula to compound this topical gel, the author noted that there have been no detailed scientific studies regarding the clinical efficacy.[16]

Another study described the use of a cutaneous piroxicam 0.5%, lidocaine 2%, and cyclobenzaprine HCl 0.5% gel for pain management prior to treatment with extracorporeal shock wave lithotripsy (ESWL) for patients with renal and ureteral stones.[17] Patients were divided into 3 groups: 1 where patients did not receive the topical analgesia and 2 where the analgesia was administered 30 and 60 minutes prior to ESWL.[17] The authors concluded that the combination therapy did improve patient compliance with ESWL compared to standard protocol, which did not involve analgesia before treatment. While administration of the gel 30 minutes before the procedure was effective, applying it 60 minutes ahead of time "significantly reduced the pain perception and the level of opioid consumption."[17]

Cyclobenzaprine was described as part of a topical compounded combination product with diclofenac 5%, ibuprofen 3%, baclofen 2%, cyclobenzaprine 2%, bupivacaine 1%, gabapentin 6%, and pentoxifylline 1% for the treatment of radicular pain.[18] The authors of this case series noted that while oral formulations of cyclobenzaprine are used for the treatment of acute back pain, their review of the literature did not find information regarding efficacy of topical or oral cyclobenzaprine formulations for neuropathic or radicular pain.[18] The authors concluded that treatment of radicular pain with the topical combination was successful, and that there is a need for a randomized, prospective study of topical agents (both single and compounded) for this indication in the future.[18]

The 2020 report on compounded topical pain creams from the National Academies of Sciences, Engineering, and Medicine concluded that there is insufficient evidence on the effectiveness of cyclobenzaprine applied topically to treat pain, limited evidence suggesting topical cyclobenzaprine has dermal penetration, and insufficient evidence for allergic contact dermatitis as a side effect.[19]

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

No studies included

Table 4. Number of studies by country

No studies included

Table 5. Summary of included studies

No studies included

Table 6. Dosage by indication – US

No studies included

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No studies included

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. Eight SMEs discussed cyclobenzaprine HCl. Amongst these 8 SMEs, there were 3 medical doctors, 1 pharmacist, 1 nurse practitioner, 2 physician assistants, and 1 dentist. The SMEs specialized and/or were board-certified in anesthesiology, internal medicine, oncology/hematology, oral and maxillofacial surgery, orthopedics, pain management, palliative care, pharmacotherapy, and rheumatology, working in academia, academic medical centers, hospitals/health systems, and private practice/clinics. The SMEs had been in practice for 8 to 34 years.

Flexeril® (cyclobenzaprine) is an oral muscle relaxant that was described as the emergency room's (ER) first line drug "because it's cheap and it works and patients take it." One SME said that they do use it topically, and that most companies provide different combinations. They agreed that there is a use for compounded topical cyclobenzaprine since it is hard to find it in regular pharmacies: "If I wanted cyclobenzaprine with gabapentin and ketamine, the pharmacy can't do it. So, I have to go to these special compounding pharmacies and it's expensive." The SME had never used cyclobenzaprine as a topical solo agent, "there's always something else in there, lidocaine, some local anesthetic base, then I add something on. If it's arthritic pain, I may want to add an anti-inflammatory. It's very, very rare to just use a muscle relaxant."

Another SME said that they first started using compounded ketoprofen and cyclobenzaprine cream for patients with musculoskeletal injuries in pilots; this patient population was prohibited to take anything oral while flying, so topical pain creams allowed their strain or sprain to be treated and for the patient to keep working without worrying about side effects, such as somnolence for cyclobenzaprine. They also reported using topical pain creams for tendonitis in the hand and elbow, and for knee and hip arthritis, mostly ketoprofen with cyclobenzaprine, sometimes with gabapentin added for numbness, tingling, or other nerve issues.

Cyclobenzaprine is not the only muscle relaxant used topically. One SME said that the "Medicare-friendly" topical preparation does not contain cyclobenzaprine; however, they did not specify what agent replaces it. Other active ingredients used in topical pain creams included benzocaine, gabapentin, ketamine, ketoprofen, and lidocaine.

Several SMEs said that they had used compounded topical creams in the past but stopped due to issues with the pharmacies that provided the products. One SME said that patients received refills that they had not requested, so they have stopped using compounded products and currently use PENNSAID® (diclofenac topical solution) and ketoprofen. The SME said that they miss the compounded products based on patient feedback and response but have patients who say that cannabidiol (CBD) cream works well.

One SME said that they use cyclobenzaprine if a patient comes in with muscle pain or trigeminal neuralgia, but not as a cream, and several said they do not see a role for topical cyclobenzaprine. Another SME said they do not use cyclobenzaprine at all.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which cyclobenzaprine HCl prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded cyclobenzaprine HCl

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

CONCLUSION

Cyclobenzaprine HCl was nominated for inclusion on the 503B Bulks List as a topical cream to treat myofascial pain. Cyclobenzaprine HCl is not available in the nominated dosage form and ROA in any of the national medical registries searched.

From the literature review and interviews, cyclobenzaprine HCl is a common API used in topical analgesics for musculoskeletal conditions, but rarely given as a solo product. Other APIs administered in combination with cyclobenzaprine HCl in topical formulations include nonsteroidal anti-inflammatory drugs and local anesthetics such as: baclofen, bupivacaine, diclofenac, gabapentin, ibuprofen, ketamine, ketoprofen, lidocaine, pentoxifylline, and piroxicam. Despite positive patient responses to administration of topical combination pain creams, some SMEs have ceased use due to issues with the pharmacies that provided the products.

Zero people responded to the survey distributed via professional medical associations and available on the project website.

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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 April 3, 2020
- Date last searched: April 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 16

1	c#clobenzaprin$.tw.	261
2	exp administration, topical/	86715
3	topical$.tw.	103235
4	transcutaneous$.tw.	14179
5	cutaneous$.tw.	148988
6	transdermal$.tw.	14298
7	derm$.tw.	237962
8	emulsions/	17705
9	exp gels/	50857
10	liniments/	123
11	ointments/	12745
12	skin cream/	985
13	emulsion?.tw.	32210
14	gel?.tw.	304409
15	liniment?.tw.	143
16	ointment?.tw.	11675
17	salve?.tw.	338
18	paste?.tw.	12184
19	unguent$.tw.	112
20	lotion?.tw.	2264

21	cream?.tw.	18553
22	or/2-21	890189
23	and/1,22	17
24	exp animals/ not humans/	4686014
25	23 not 24	16
26	limit 25 to english language	16

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 109

1	cyclobenzaprine'/de	2099
2	cyclobenzaprin*':ti,ab,tn	479
3	ciclobenzaprin*':ti,ab,tn	3
4	#1 OR #2 OR #3	2131
5	topical drug administration'/exp	110865
6	topical treatment'/de	12462
7	topical*':ti,ab	146566
8	cutaneous*':ti,ab	213902
9	transdermal*':ti,ab	20865
10	derm*':ti,ab	372946
11	cream'/de	9201
12	gel'/exp	73810
13	liniment'/de	248
14	lotion'/de	2810
15	ointment'/exp	18393
16	paste'/de	2490
17	salve'/de	165
18	emulsion'/exp	44335
19	cream$':ti,ab	29070
20	emulsion$':ti,ab	44035
21	lotion$':ti,ab	3945
22	ointment$':ti,ab	21306

23	paste$':ti,ab	14665
24	salve$':ti,ab	470
25	unguent*':ti,ab	239
26	liniment*':ti,ab	239
27	gel$':ti,ab	357854
28	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #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	1214383
29	#4 AND #28	115
30	[animals]/lim NOT [humans]/lim	6013410
31	#29 NOT #30	109
32	#29 NOT #30 AND [english]/lim	109

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded cyclobenzaprine HCl. 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 cyclobenzaprine HCl to your patients?

   - o Yes
   - o No

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

   - o Topical cream
   - o None of the above

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

   - o Myofascial pain
   - o Other (please explain) _____

5. I use compounded cyclobenzaprine HCl 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 cyclobenzaprine HCl.
   - o Other (please explain) _____

6. Do you stock non-patient-specific compounded cyclobenzaprine HCl at your practice?

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

7. I obtain compounded cyclobenzaprine HCl 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.