Summary Report

Ergotamine tartrate

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
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 ergotamine tartrate (UNII code: MRU5XH3B48), 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 ergotamine tartrate 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 ergotamine tartrate 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 ergotamine tartrate 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

Ergotamine tartrate was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy. Ergotamine tartrate was nominated for treatment of headache and migraine via a topical or mucosal cream, gel, or ointment in various strengths from 0.025% to 0.1%.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of ergotamine tartrate.[6-9]

Reasons provided for nomination to the 503B Bulks List included ergotamine tartrate being temporarily unavailable by the manufacturer and excipients from tablets not being appropriate for topical application.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of ergotamine tartrate 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 ergotamine tartrate; name variations of ergotamine tartrate 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 ergotamine tartrate. 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: ergotamine tartrate and topical or mucosal 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 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 ergotamine tartrate 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 ergotamine tartrate 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 ergotamine tartrate 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 ergotamine tartrate 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 ergotamine tartrate; setting; total number of patients; number of patients who received ergotamine tartrate; patient population; indication for use of ergotamine tartrate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of ergotamine tartrate in a combination product; use and formulation of ergotamine tartrate in a compounded product; use of ergotamine tartrate 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 ergotamine tartrate 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 ergotamine tartrate: neurology, 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 ergotamine tartrate 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

- Ergotamine tartrate is not available as an FDA-approved product in the nominated dosage form and ROA.
- Ergotamine tartrate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for ergotamine tartrate.
- Ergotamine tartrate is not available in the nominated dosage form and ROA in any of the foreign 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 148 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 129 titles and abstracts were screened. After screening, the full text of 17 articles was reviewed. Finally, 0 studies were included. Seventeen studies were excluded for the following reason: wrong study design (17 studies).

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 ergotamine tartrate

No studies were included from the literature review.

Pharmacology and historical use

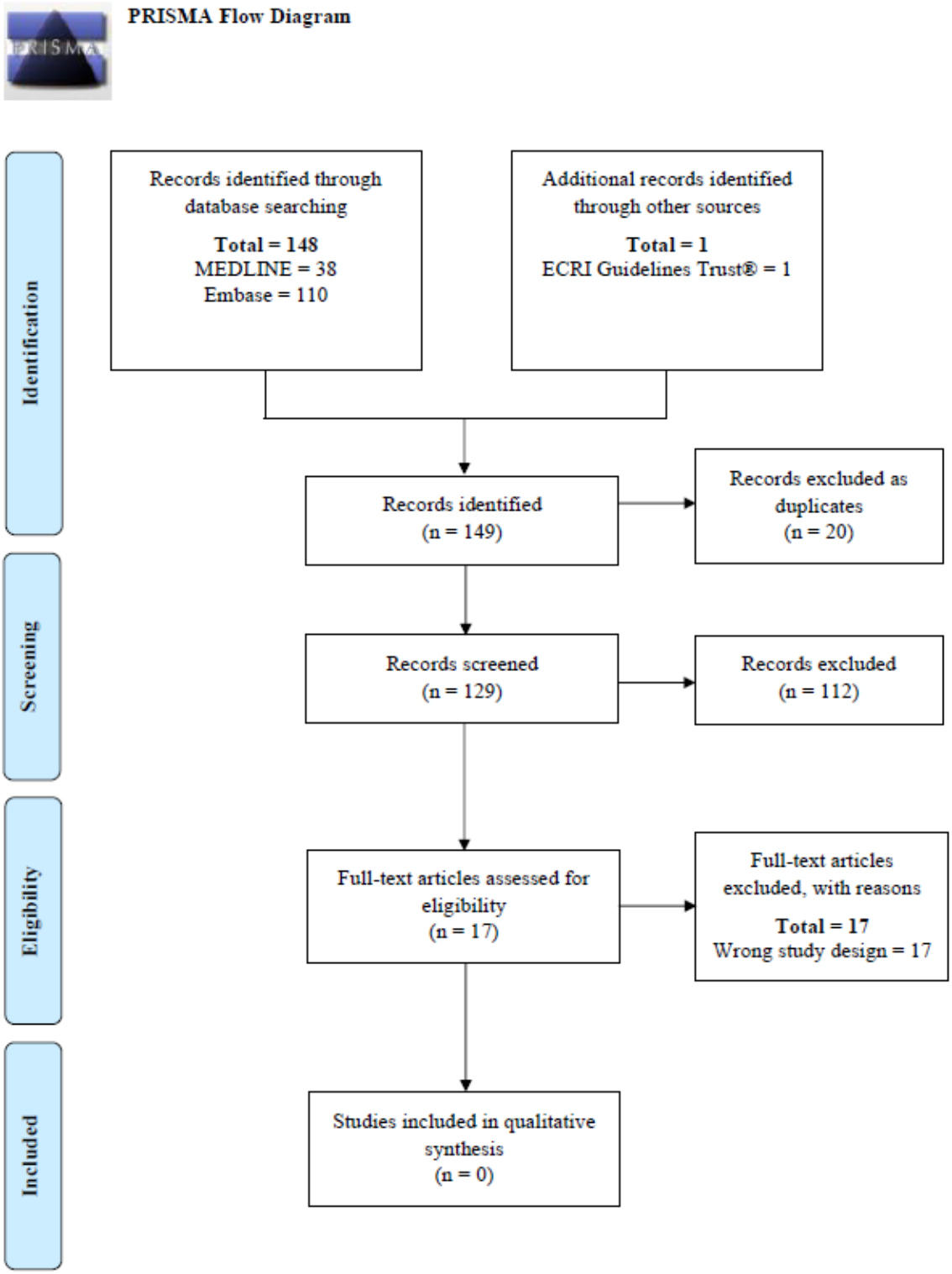
Several studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of ergotamine tartrate. Ergotamine tartrate is an alkaloid derived from the ergot fungus *Claviceps purpurea*.[10] Ergotamine tartrate has pharmacological activity at multiple central and peripheral sites, including 5-hydroxytryptamine (5-HT) receptors, α-adrenergic receptors and dopaminergic receptors. The action of ergotamine tartrate at these receptors causes vasoconstriction and depression of central vasomotor centers thereby providing relief for vascular headaches, such as migraines and cluster headaches.[11-14] Ergotamine tartrate is often administered in combination with caffeine, which potentiates vasoconstriction and may enhance gastrointestinal absorption of ergotamine tartrate.[13,15,16] The bioavailability of

ergotamine tartrate varies considerably depending on the ROA, with low bioavailability for oral, sublingual, and rectal administration (< 5%) and significantly higher bioavailability for parenteral (intravenous or intramuscular) administration.[10,15,17] Currently, ergotamine tartrate is available in the US as a single-agent sublingual tablet, and in combination with caffeine as an oral tablet and rectal suppository.

Ergotamine tartrate has been used since the 1920s for the treatment of vascular headaches.[9,16] In a 1972 review on drug therapy for migraines, the author called ergotamine tartrate "the most effective treatment" for an acute migraine attack but went on to write that "these agents [ergot alkaloids] are specific only for migraine and have no place in treatment of other types of headaches."[18] Several review articles from the 1990s recommended the use of ergotamine tartrate for the treatment of acute migraine attacks or cluster headaches.[12,14-16,19-23] In a 1999 review, Cerbo et al stated that "Until recently, ergotamine tartrate preparations were the most widely accepted treatments of choice for the prevention and treatment of CH [cluster headache] attacks."[12] More recently, the authors of a 2018 review on the treatment of acute migraine observed that while "most physicians feel there is some place for ergotamine in the acute treatment of migraine…there is no consensus as to its place in clinical practice."[17] Possible roles for ergotamine in the acute treatment of migraine included patients who were prescribed ergotamine prior to the use of triptans and have experienced a positive response, patients with attacks that last more than 48 hours, and patients with frequent recurrence of headaches. In the 2019 edition of *Aids to management of headache disorders in primary care*, the Global Campaign against Headache and the European Headache Federation stated that the use of ergotamine should be avoided in the acute or symptomatic management of episodic migraine, calling ergotamine "a poor substitute for triptans" with low and unpredictable bioavailability and poor tolerability.[24] The authors of this statement concluded that ergotamine is "no longer recommended for routine use" in the acute or symptomatic management of episodic migraine.[24]

Ergotamine tartrate's lack of receptor specificity contributes to a range of side effects associated with its use, including nausea, vomiting, leg weakness, and precordial chest pain.[13,17,18] The nausea and vomiting associated with ergotamine tartrate may further exacerbate the nausea and vomiting symptoms associated with migraines. One author noted that patients "exhibit significant differences in their susceptibility to ET [ergotamine tartrate]-associated nausea."[16] Strategies to prevent or alleviate the nausea and vomiting associated with ergotamine tartrate include pre- or concurrent treatment with an antiemetic, reducing the dose of ergotamine tartrate, and/or administering ergotamine tartrate as early as possible during a migraine attack.[9,17,19] Overuse of ergotamine tartrate (excessive dosage or chronic use) may lead to drug-induced headache, ischemia and ergotism.[13,19,24] The authors of several reviews on the use of ergotamine tartrate in the treatment of migraine or cluster headaches noted that the dose and frequency of ergotamine tartrate should be limited to prevent overuse.[14,15,19,22]

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

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 combinations

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. Five SMEs discussed ergotamine tartrate. Amongst these 5 SMEs, there were 4 medical doctors and 1 physician assistant. The SMEs specialized and/or were board-certified in neurology, pediatrics, and primary care and family medicine, working in academic medical centers and private practice/clinics. The SMEs had been in practice for 11 to 30 years.

The treatment of migraines requires a comprehensive and multidisciplinary approach. Lifestyle modifications, including sleep, hydration, diet, exercise, and stress management, are the focus initially. Patients with migraines are also traditionally low in magnesium so supplementation may be started early in treatment as well. Other nutraceuticals, like vitamin B2, melatonin, and coenzyme Q10, also play a role in the treatment approach. If after approximately 1-3 months the lifestyle modifications and nutraceuticals are not sufficient to stop the migraines, then the next step is to start a medication. However, lifestyle modifications still play a vital role in care with one SME stating that "no matter what you do, whether it's meds [medications], nutraceuticals etc, if you don't do the lifestyle things, they're not going to work." The SME referenced the Childhood and Adolescent Migraine Prevention (CHAMP) trial that compared the efficacy of amitriptyline, topiramate, and placebo to prevent pediatric migraines.[25] The trial was stopped early due to no difference being found between any of the groups. The SME stated that this trial highlights that while there is evidence to support the use of certain medications, "there's more to it than just that" continuing that "I make the point that they [the patient] need to do their part [lifestyle changes] so I can do my part [prescribing medications]."

Once the decision is made to initiate drug therapy, then there are two categories that are utilized: prophylactic therapy that is taken regularly to prevent migraines from occurring and acute therapy to abort a migraine once it has started. Depending on the number and severity of headaches the patient is having and how the headaches are impacting the patient's daily life, treatment may focus on acute therapy or a combination of preventative therapy with a rescue medication. Ergotamine, along with other ergot alkaloids like dihydroergotamine (DHE) and methylergonovine (Methergine®), are used as rescue medications. One SME stated that they regularly use DHE for inpatients and, depending on how the patient responds, will prescribe Migranal® (dihydroergotamine) or another ergot alkaloid. The SME will also use a short course of Methergine® with their older patients that respond well to DHE; however, patients generally do not tolerate it, so the SME does not use it often.

None of the SMEs had used ergotamine as a topical product. Ergotamine is associated with several concerning side effects and one SME stated they stopped using it years ago due to dystonic reactions. Two SMEs stated that if a topical product can lessen the risk of side effects, then they would see a benefit. The SMEs also thought that a fast-acting, quick-absorbing form could be useful and that it "would be something worthwhile" to try, assuming it was effective. One SME pointed out that "because so many patients have nausea, vomiting, and GI symptoms, they do not want pills," and there are challenges with the nasal sprays due to incorrect administration technique. The subcutaneous injections are not generally preferred, especially in pediatric patients. Another SME stated that "you want your patient to know that you are with them on this journey," and that more treatment options make it easier to find a solution.

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 ergotamine tartrate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded ergotamine tartrate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded ergotamine tartrate

No respondents to survey distributed via professional medical associations

CONCLUSION

Ergotamine tartrate was nominated for inclusion on the 503B Bulks List as a topical or mucosal cream, gel, and ointment to treat migraine and headache. Ergotamine tartrate is not available in the nominated dosage form and ROA in any of the national medical registries searched.

No studies were included from the literature review. However, several studies were found that provided valuable background information on the pharmacology and historical use of ergotamine tartrate. Ergotamine tartrate has been administered, either alone or in combination with caffeine, orally, rectally and parenterally for the treatment of vascular headaches since the 1920s. Several review articles from the 1990s recommended the use of ergotamine tartrate for the treatment of acute migraine attacks or cluster headaches. While the literature shows that some clinicians still feel there is a place for ergotamine tartrate in the treatment of migraines and headaches, the poor oral and rectal bioavailability, and tolerability in some patients of ergotamine tartrate, along with the risk of overuse, led the Global Campaign against Headache and the European Headache Federation to conclude in 2019 that ergotamine should no longer be recommended for routine use.

None of the SMEs had used ergotamine as a topical product and several expressed concerns about the side effects associated with ergotamine. However, the general consensus amongst the SMEs was that the more options available for patients, the better, so it might be beneficial to have ergotamine tartrate available as a topical product, but they could not guarantee the effectiveness.

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 March 23, 2020
- Date last searched: March 24, 2020
- Limits: Humans (search hedge); English language
- Number of results: 38

1	ergotamine/	2304
2	ergotamin$.tw.	1725
3	or/1-2	3006
4	exp administration, topical/	86627
5	topical$.tw.	103077
6	percutaneous$.tw.	141643
7	cutaneous$.tw.	148817
8	transdermal$.tw.	14278
9	derm$.tw.	237626
10	mucosal$.tw.	118072
11	mucous$.tw.	22634
12	gels/	28601
13	liniments/	122
14	ointments/	12746
15	skin cream/	983
16	gel?.tw.	304164
17	liniment?.tw.	143
18	ointment?.tw.	11661
19	salve?.tw.	338
20	paste?.tw.	12162

21	unguent$.tw.	111
22	lotion?.tw.	2265
23	cream?.tw.	18521
24	or/4-23	1088516
25	and/3,24	67
26	exp animals/ not humans/	4681428
27	25 not 26	57
28	limit 27 to english language	38

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: 110

1	ergotamine tartrate'/de	1669
2	ergotamin*':ti,ab,tn	2873
3	#1 OR #2	3880
4	topical drug administration'/exp	110771
5	topical*':ti,ab	146272
6	cutaneous*':ti,ab	213519
7	transdermal*':ti,ab	20815
8	derm*':ti,ab	372207
9	percutaneous*':ti,ab	216395
10	mucosal*':ti,ab	167917
11	mucous*':ti,ab	38200
12	cream'/de	9180
13	gel'/exp	73480
14	liniment'/de	248
15	lotion'/de	2804
16	ointment'/exp	18376
17	paste'/de	2490
18	salve'/de	165
19	cream$':ti,ab	29020
20	liniment$':ti,ab	231
21	lotion$':ti,ab	3941
22	ointment$':ti,ab	21285

23	paste$':ti,ab	14635
24	salve$':ti,ab	469
25	unguent*':ti,ab	239
26	gel$':ti,ab	357380
27	#4 OR #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	1548956
28	#3 AND #27	163
29	[animals]/lim NOT [humans]/lim	6007063
30	#28 NOT #29	142
31	#28 NOT #29 AND [english]/lim	110

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded ergotamine tartrate. 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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer ergotamine tartrate to your patients?

   - ○ Yes
   - ○ No

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

   - ○ Mucosal cream
   - ○ Mucosal gel
   - ○ Mucosal ointment
   - ○ Topical cream
   - ○ Topical gel
   - ○ Topical ointment
   - ○ None of the above

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

   - ○ Headache
   - ○ Migraine
   - ○ Other (please explain) _____

5. I use compounded ergotamine tartrate 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 ergotamine tartrate.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded ergotamine tartrate at your practice?

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

7. I obtain compounded ergotamine tartrate 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.