

Summary Report

Tetracaine

Prepared for:

Food and Drug Administration

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

Grant number: 2U01FD005946

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)

University of Maryland School of Pharmacy

February 2020

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling \$2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

REVIEW OF NOMINATIONS	4
METHODOLOGY	4
Background information.....	4
Systematic literature review.....	5
Outreach to medical specialists and specialty organizations	7
Survey.....	7
CURRENT AND HISTORIC USE.....	8
Summary of background information	8
Summary of literature review	10
Summary of focus groups/interviews of medical experts and specialty organizations	14
Summary of survey results.....	15
CONCLUSION.....	16
APPENDICES	17
Appendix 1. References.....	17
Appendix 2. Survey instrument	19

Table of Tables

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

REVIEW OF NOMINATIONS

Tetracaine (UNII code: 0619F35CGV) was nominated for inclusion on the 503B Bulks List by David Smith, AnazaoHealth, Outsourcing Facilities Association (OFA), and Sincerus Florida, LLC as a topical numbing agent, specifically as topical anesthesia for application prior to dermatological procedures. Additionally, OFA stated that the exact medical condition is generally unknown, tetracaine is generally used for topical local analgesia for superficial dermatological procedures.

Tetracaine will be compounded as a 4-10% topical cream, emulsion, and ointment and as a 2-6% oral dental gel in combination with prilocaine and lidocaine. Additionally, per the prescriber's request other topical dosage forms in various strengths may be compounded; the therapeutic dose ranges from 4-10%.

Tetracaine was nominated for use in combination use with additional active pharmaceutical ingredients (API), refer to Table 7 for the specific nominated combination formulations.

Reasons provided for nomination to the 503B Bulks List include:

- The compounded product is a different dosage form and route of administration than the FDA-approved ophthalmic solution. The product being requested is also at concentrations higher than the available 0.5% ophthalmic solution.
- Prescribers have requested combinations and strengths of topical anesthetics not commercially available. For example, there is no FDA-approved drug combining tetracaine with prilocaine and lidocaine as a topical gel or tetracaine combined with lidocaine and benzocaine.
- There is a need for numbing the dermal layer of skin prior to topical chemical peel and laser treatments for patient comfort. The commercially available product has only two (2) APIs and is not as effective as the compounded product.
- Compounding from bulk drug substances means starting from the active pharmaceutical ingredient (API) in its purest form without any fillers, excipients, binders, dyes, preservatives, or other materials. Patient sensitivities to inactive ingredients found in commercially available products may lead to treatment failure.
- Variance in the API of finished products may introduce unacceptable inaccuracies into the compounding product; compounding from the bulk substance is more accurate.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of tetracaine 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: United States, 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 tetracaine; name variations of tetracaine were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing tetracaine. 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 10, 2019. The search included a combination of (tetracaine[TIAB] OR amethocaine[TIAB]) AND (prilocaine[TIAB] OR lidocaine[TIAB] OR benzocaine[TIAB] OR phenylephrine[TIAB]) AND (gel OR cream OR emulsion OR ointment OR topical* OR dental* OR solution) AND (treat*[TIAB] OR therap*[TIAB] OR clinic*[TIAB] OR aneste*[TIAB]) AND humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Tetracaine is a component of an FDA-approved product, as a result, articles were excluded if tetracaine was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Additional exclusion criteria includes any dosage form/ROA that differed from the nominated dosage form/ROA. Articles were considered relevant based on the identification of a clinical use of tetracaine or the implementation of tetracaine in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

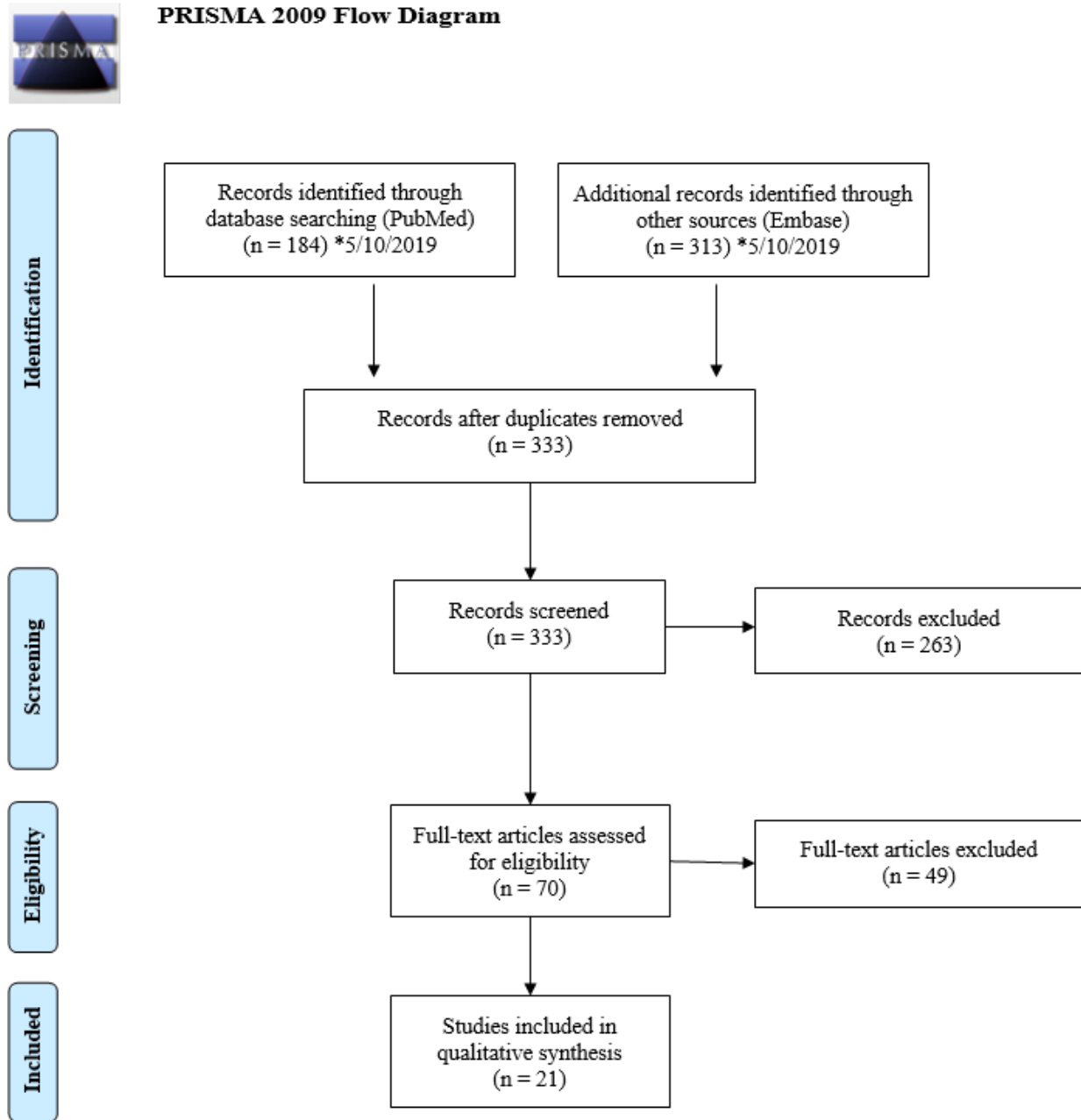
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for tetracaine 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 tetracaine 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, six (6) medical specialties that would potentially use tetracaine were identified: anesthesiology, dermatology, pain management, primary care, surgery, and wound care. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Three (3) experts were contacted for interviews, of which three (3) accepted and zero (0) declined. Two (2) experts were interviewed at the same time. One (1) interview was recorded and transcribed via ©Rev.com, while the other interview was not recorded. 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 anesthesiology, dermatology, pain management, primary care, surgery, and wound care, identified from the nominations, literature review, and interviews, 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 12 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)
Pain Medicine	American Academy of Pain Medicine (AAPM)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Anesthesiology	American Society of Anesthesiologists (ASA)	Declined, requires a PI who is an ASA member
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Surgery	American College of Surgeons (ACS)	Failed to respond
Wound Care	American Professional Wound Care Association (APWCA)	Failed to respond
	Wound Healing Society (WHS)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Tetracaine is available as an FDA-approved product.
- Tetracaine is available in various topical dosage forms as an OTC product in the US.
- There is a current United States Pharmacopeia monograph for tetracaine.
- Tetracaine is available in Abu Dhabi, Belgium, Canada, Hong Kong, Ireland, New Zealand, and UK.

Table 3. Currently approved products – US^a

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date
Tetracaine / Lidocaine	7% / 7%	Cream	Topical	Prescription	06/29/2006
Tetracaine / Lidocaine	70mg / 70mg	Patch	Topical	Prescription	06/23/2005

Abbreviation: ROA, route of administration.

^aSource: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

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

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date ^b
Tetracaine	4%	Gel	Topical	Canada	Ethical	03/16/1998
				Ireland	Pharmacy-only ^c	07/6/2018
				New Zealand	Pharmacy-only ^c	10/28/1999
				UK	Pharmacy-only ^c	10/7/1995
Tetracaine HCl	0.5%	–	–	Abu Dhabi	–	–
Tetracaine / Benzocaine	2% / 18%	Gel	Buccal, oral, topical	Canada	Ethical	12/31/1992
				New Zealand	Prescription	10/21/2010
Tetracaine / Lidocaine	7% / 7%	Cream, medicated plaster	Cutaneous, topical	Belgium	Prescription	10/19/2008
				Canada	Prescription	09/28/2015
				Hong Kong	Prescription	07/15/2015
				Ireland	Prescription-only non-renewable	01/25/2008

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

^aMedicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, route of administration and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or routes of administration similar to those requested in the nominations. See Methodology for full explanation.

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

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

Summary of literature review

- Total number of studies included: 21 studies (9 descriptive and 12 experimental).
- Most of the studies were from the US (16).
- The nominated combination formulations were identified in 13 articles.
- The most common indication for the use of tetracaine in the US and non-US studies was anesthesia.
- Compounded products were identified from both US (4% cream, 4% gel, and 4% ointment) and non-US studies (4% cream and 4% gel) for anesthesia.

Table 5. Types of studies

Types of Articles	Number of Studies
Descriptive ¹⁻⁹	9
Experimental ¹⁰⁻²¹	12
Observational	0

Table 6. Number of studies by country

Country	Number of Studies
Malaysia ²¹	1
Spain ¹¹	1
The Netherlands ²⁰	1
UK ^{13,14}	2
US ^{1-10,12,15-19}	16
Total US: 16 Total non-US Countries: 5	

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Tetracaine 4-10% / Not mentioned – topical cream, emulsion, ointment ^{2,3,7,9,11} <ul style="list-style-type: none"> • Tetracaine 2.5% / Lidocaine 2.5% – topical cream¹¹ • Tetracaine 8% / Lidocaine 8% – topical cream³ • Tetracaine 5% / Benzocaine 20% / Lidocaine 6% – topical² • Tetracaine 6% / Benzocaine 20% / Lidocaine 6% – vaginal⁷ • Tetracaine 6% / Benzocaine 20% / Lidocaine 6% +/- Diphenhydramine 2% – topical cream⁹ 	5
	Tetracaine 6% / Lidocaine 6% – topical cream, emulsion, gel, ointment, solution ¹	1
	Tetracaine 7% / Lidocaine 7% – topical cream, emulsion, gel, ointment, solution	0
	Tetracaine 7% / Lidocaine 23% – topical cream, emulsion, gel, ointment, solution ^{4,16}	2
	Tetracaine 4% / Benzocaine / Lidocaine – topical cream ^{5,6,8,10,15} <ul style="list-style-type: none"> • Tetracaine 4% / Benzocaine 10% / Lidocaine 6% – topical cream⁸ • Tetracaine 4% / Benzocaine 20% / Lidocaine 6% – topical cream^{5,6,15}, ointment¹⁰ 	5
	Tetracaine 4% / Benzocaine 20% / Lidocaine 8% – topical cream, emulsion, gel, ointment, solution	0
	Tetracaine 10% / Benzocaine 20% / Lidocaine 10% – topical cream, emulsion, gel, ointment, solution	0
	Tetracaine 10% / Lidocaine 20% / Phenylephrine HCl 0.05% – topical cream, emulsion, gel, ointment, solution	0
	Tetracaine 2-6% / Lidocaine varies / Prilocaine varies – oral, dental gel	0
Others found in literature	Tetracaine 1% / Lidocaine 1% / Phenylephrine 2.5% – topical ^{18,19}	2
	Tetracaine 4% / Lidocaine 20% / Phenylephrine 2% – intraoral gel ¹⁷	1

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Anesthesia ^{1-10,12,15-19}	–	1-7%	–	Topical	Once
		4-8%	Cream		
		4%	Gel		
		4%	Ointment		
		6%	Paste		
	–	6%	–	Vaginal	Once
			Gel		

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Anesthesia ^{11,13,14,20,21}	–	2.5-4%	Cream	Topical	Once
		4%	Gel		

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Anesthesia ^{2,6,8-10,16,17}	2003-2018	• Compounded tetracaine 5%, benzocaine 20%, lidocaine 6% ²	–	5%
		• Tetracaine 4%, benzocaine 20%, lidocaine 6% ^{6,10}	Gel, ointment	4%
		• Compounded tetracaine 4%, benzocaine 10%, lidocaine 6% ⁸	Cream	4%
		• Tetracaine 4%, benzocaine 20%, lidocaine 6% compounded with diphenhydramine 2% ⁹	Cream	4%
		• Compounded tetracaine 7%, lidocaine 23% ¹⁶	–	7%
		• Tetracaine 4%, lidocaine 20%, phenylephrine 2% from pharmacy ¹⁷	Gel	4%

Abbreviation: “–”, not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Anesthesia ^{14,20}	• Tetracaine 4% w/w in carbomer 1.5% w/w ¹⁴	Gel	4%
	• Tetracaine base 4 g, sorbitan oleate 0.2 mL, polysorbate 80 0.2 mL, arachis oil 10 g, and carbomer 934P 1% gel 86 g compounded by the pharmacy ²⁰	Cream	

Summary of focus groups/interviews of medical experts and specialty organizations

Three (3) medical experts were interviewed.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Tetracaine	Interview Summary Response
ANE_01	MD	Anesthesiology	Trauma center	Not specified	<ul style="list-style-type: none"> Interested in having access to compounded “caine” products Currently uses compounded lidocaine, epinephrine, and tetracaine cream
ANE_02	NP	N/A	Trauma center	Not specified	<ul style="list-style-type: none"> Interested in having access to compounded “caine” products Currently uses compounded lidocaine, epinephrine, and tetracaine cream
DER_06	MD	Dermatology/ Immunology	Independent consultant	Not specified	<ul style="list-style-type: none"> Believes there is a need for office stock, used a lot for anesthesia before procedures Provider’s preferences for particular formulations and some need different onset of action

Abbreviations: MD, Doctor of Medicine; NP, Nurse Practitioner.

Indications for use

- One (1) interviewee stated that the caines are used a lot in physician’s office as pre-anesthesia, especially for cosmetic procedures.

Use of compounded tetracaine

- The concentration and/or combinations prescribers want depends on where and how they were trained.
- Varying onset of actions needed
 - Commercially available products are limited to one concentration and may not provide the longer-lasting anesthesia needed for some procedures.

Need for office stock:

- The “caines” are commonly used in the physician’s office. One (1) interviewee expressed, “I think that these have a role in the office. To the best of my knowledge, people who use them are well-trained and skilled and cognizant of the adverse events and I think we should work to try to continue to make them available.

- Safer and convenient in office
 - Do not need to rely on patients getting the prescription filled before getting their procedure.
 - The interviewee also preferred “people be in a super monitored or supervised environment where they’re going to be having this applied.”
 - There are central nervous system (CNS) adverse events, and the interviewee said that, “we have to assume the physicians actually pay attention to knowing and understanding the risks associated with all of these medicines.”

Summary of survey results

Table 13. Characteristics of survey respondents [10 people responded to the survey^a]

Board Certification	MD	PhD	No Response
Anesthesiology	1	0	0
Dermatology	1	0	0
Neurology	1	0	0
Pain Medicine	2	0	0
No Board Certification	0	1	1
No Response	0	0	4

Abbreviations: MD, Doctor of Medicine; PhD, Doctor of Philosophy.

^aSome respondents reported more than one terminal clinical degree or board certification.

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

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

^aOut of ten (10) respondents, one (1) reported using, prescribing, or recommending a tetracaine product.

Table 15. Compounded use of tetracaine in practice

No survey respondents provided this information

Table 16. Indications for which tetracaine 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 tetracaine usage over the past 5 years

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

CONCLUSION

Tetracaine (UNII code: 0619F35CGV) was nominated for inclusion on the 503B Bulks List for use as a topical numbing agent, specifically as topical anesthesia for application prior to dermatological procedures. Tetracaine will be compounded as a 4-10% topical cream, emulsion, and ointment and as a 2-6% oral dental gel in combination with prilocaine and lidocaine.

Tetracaine is available as an FDA-approved product and in various topical dosage forms as an OTC product in the US. It is also available in Abu Dhabi, Belgium, Canada, Hong Kong, Ireland, New Zealand, and UK.

From the literature review, the most common indication for the use of tetracaine in the US and non-US studies was anesthesia. Nominated combination products were found in 13 articles. Compounded products were identified from both US (4% cream, 4% gel, and 4% ointment) and non-US studies (4% cream and 4% gel).

From the interviews, two (2) interviewees were interested in having access to compounded “caine” products and currently use compounded lidocaine, epinephrine, and tetracaine cream. The other interviewee believed there is a need for office stock as the “caines” are often used for anesthesia before procedures. The combination and/or concentration used depends on the provider’s preferences.

From the survey responses, one (1) out of ten (10) respondents used tetracaine. No further information was provided for how tetracaine was used.

APPENDICES

Appendix 1. References

1. Admani S., Ortiz A. Effect of hybrid 2940nm and 1470nm intravaginal laser treatment on stress urinary incontinence. *Lasers Surg Med.* 2017;49:62-63. doi:10/gf4b95
2. Brightman L., Brauer J., Geronemus R., et al. 3-dimensional evaluation of a minimally invasive fractional bipolar radiofrequency device for lifting and volumizing of the face. *Lasers Surg Med.* 2012;44:12-13. doi:10/gf4b93
3. Grubbs H., Robb C.W. Successful use of a fractional 2940nm laser in treating chronic, severe erosive pustular dermatosis of the scalp. *Lasers Surg Med.* 2018;50(4):389. doi:10/gf22sh
4. Kauvar A.N., Singh G. Combination, sequential treatment using fractionated 1550 nm, fractionated 1927nm and picosecond 532nm lasers improves moderately severe photodamage in a single treatment session. *Lasers Surg Med.* 2019;51:S26. doi:10/gf4b96
5. Knight J..M. Synergistic sequential treatment (SST) combining fractional nonablative laser and intense pulsed light for skin rejuvenation. *J Am Acad Dermatol.* 2016;74(5):AB24.
6. Lee M.-W.C. Topical triple-anesthetic gel compared with 3 topical anesthetics. *Cosmet Dermatol.* 2003;16(4):35-38.
7. Rubin R.S., Winter A.G., Minton J.N., Gagno C., Goldstein I. Peri-clitoral botulinum toxin as a treatment for persistent genital arousal disorder (PGAD). *J Sex Med.* 2017;14(6):e364.
8. Singh S., Peterson J., Friedman P. Management of mild to moderate rhinophyma with ablative fractional photothermolysis. *J Am Acad Dermatol.* 2013;68(4):AB225. doi:10/f2k3b5
9. Wendt J., Chidester J., Gupta S. An evaluation of antihistamine pre-treatment in facial injectable treatments. *J Investig Med.* 2016;64(1):295. doi:10.1136/jim-d-15-00013.369
10. Beer K.R., Lupo M. The efficacy, safety, and subject satisfaction of pain management of a selfocclusive topical anesthetic cream during and after filler injections for the correction of nasolabial folds. *J Am Acad Dermatol.* 2014;70(5):AB21. doi:10/gf22r9
11. Cárceles MD., Alonso JM., García-Muñoz M., Nájera MD., Castaño I., Vila N. Amethocaine-lidocaine cream, a new topical formulation for preventing venopuncture-induced pain in children. *Reg Anesth Pain Med.* 27(3):289-295. doi:10/dhw397
12. Hopp C., Goebel W., Hildebolt C., Rotter B. Clinical efficacy of tetracaine anesthetic paste. *Gen Dent.* 60(2):e69-73.
13. Lawson R.A., Smart N.G., Gudgeon A.C., Morton N.S. Evaluation of an amethocaine gel preparation for percutaneous analgesia before venous cannulation in children. *Br J Anaesth.* 1995;75(3):282-285. doi:10/gf4b9z
14. McCafferty D.F., Woolfson A.D., Handley J., Allen G. Effect of percutaneous local anaesthetics on pain reduction during pulse dye laser treatment of portwine stains. *Br J Anaesth.* 1997;78(3):286-289. doi:10/gf4b92
15. Oni G., Rasko Y., Kenkel J. Topical lidocaine enhanced by laser pretreatment: a safe and effective method of analgesia for facial rejuvenation. *Aesthet Surg J.* 2013;33(6):854-861. doi:10/f46f49

16. Palm M., Misell L. Blinded comparison trial of lidocaine 4% and benzocaine 20% in a novel transdermal delivery system versus compounded lidocaine/tetracaine (23%/ 7%) for pain mitigation during microfocused ultrasound with visualization treatment. *Lasers Surg Med.* 2018;50(4):378. doi:10/gf22sh
17. Reznik DS., Jeske AH., Chen JW., English J. Comparative efficacy of 2 topical anesthetics for the placement of orthodontic temporary anchorage devices. *Anesth Prog.* 2009;56(3):81-85. doi:10/dk8prc
18. Smith GA., Strausbaugh SD., Harbeck-Weber C., Cohen DM., Shields BJ., Powers JD. Tetracaine-lidocaine-phenylephrine topical anesthesia compared with lidocaine infiltration during repair of mucous membrane lacerations in children. *Clin Pediatr (Phila).* 1998;37(7):405-412. doi:10/fsg3cb
19. Smith GA., Strausbaugh SD., Harbeck-Weber C., Cohen DM., Shields BJ., Powers JD. New non-cocaine-containing topical anesthetics compared with tetracaine-adrenaline-cocaine during repair of lacerations. *Pediatrics.* 1997;100(5):825-830. doi:10/dsgmbb
20. van Kan HJ., Egberts AC., Rijnvos WP., ter Pelkwijk NJ., Lenderink AW. Tetracaine versus lidocaine-prilocaine for preventing venipuncture-induced pain in children. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm.* 1997;54(4):388-392. doi:10/gf4b9x
21. Yeoh C.N., Lee C.Y. Pain during venous cannulation: Double-blind, randomized clinical trial of analgesic effect between topical amethocaine and eutectic mixture of local anesthetic. *J Anaesthesiol Clin Pharmacol.* 2012;28(2):205-209. doi:10/gf4b94

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 **tetracaine**. 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: Tetracaine

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

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

Display This Question:

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

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

Display This Question:

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

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

- Tetracaine 4-10% / Benzocaine 20% / Lidocaine 8-10%
- Tetracaine 6-7% / Lidocaine 6-23%
- Tetracaine 10% / Lidocaine 20% / Phenylephrine HCl 0.05%
- Tetracaine 2-6% / Lidocaine / Prilocaine
- Other (please describe) _____

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

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

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

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

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

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) _____