Summary Report

Promethazine 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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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
PLO	Pluronic lecithin organogel
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 promethazine hydrochloride (promethazine HCl; UNII code: R61ZEH7I1I), 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 promethazine 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 promethazine 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 promethazine 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 NOMINATIONS

Promethazine HCl was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA), Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy.

Promethazine HCl was nominated for allergic rhinitis, hyperemesis gravidarum, motion sickness, nausea and vomiting (including pregnancy-induced, procedural, and post-operation), nystagmus, postoperative pain, sedation, and pruritus via a 0.5-50 mg/mL topical gel and a 0.5-25 mg/mL intravenous and intramuscular injection.

Nominators provided a reference from published peer-reviewed literature to describe the pharmacology and support the clinical use of promethazine HCl.[6]

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength that is not available commercially. The approved products are injections, oral tablets or liquids, and rectal suppositories. The compounded drug product contains promethazine HCl 25 mg/mL in a topical gel. Patients experiencing nausea and vomiting may not be able to tolerate oral administration and patients with diarrhea may not tolerate rectal suppositories. Specifically, these formulations are not preferred in pediatrics who are actively experiencing nausea, vomiting, or diarrhea.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.

- According to SSPS, in order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of promethazine 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 promethazine HCl; name variations of promethazine 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 promethazine 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: promethazine HCl and topical administration (refer to Appendix 1 for full search strategies). Due to the availability of FDA-approved single-agent injectable promethazine HCl products, intravenous and intramuscular administration were not included in the literature review. 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 29, 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 29, 2020 for clinical practice guidelines that recommended the use of promethazine HCl 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 promethazine 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 promethazine 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 promethazine 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 promethazine HCl; setting; total number of patients; number of patients who received promethazine HCl; patient population; indication for use of promethazine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of promethazine HCl in a combination product; use and formulation of promethazine HCl in a compounded product; use of promethazine 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 promethazine HCl was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use promethazine HCl: allergy and immunology, neurology, obstetrics and gynecology, pediatrics and neonatology, primary care and internal medicine, and surgery. 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 promethazine 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

- Promethazine HCl is available as an FDA-approved product in the nominated dosage form and ROA.
- Promethazine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for promethazine HCl.
- Promethazine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, New Zealand, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date
Promethazine HCl	25-50 mg/mL	Solution	Injection	Prescription	Prior to 1/1/1982

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date
Promethazine HCl	25 mg/mL	Solution	Injection	Abu Dhabi	–	–
				Australia	Prescription	10/8/1991
				New Zealand	Prescription	9/7/1989
				UK	Prescription	3/16/1973

Abbreviation: "– ", not mentioned.

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

Results of literature review

Study selection

Database searches yielded 369 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 275 titles and abstracts were screened. After screening, the full text of 15 articles was reviewed. Finally, 1 study was included. Fourteen studies were excluded for the following reasons: wrong study design (8 studies); promethazine HCl only mentioned briefly (4); wrong dosage form or ROA (1); promethazine HCl not used clinically (1).

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

Characteristics of included studies

There was 1 included US case report published in 2009.[7]

The outcome measured was resolution of nausea and vomiting.

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

Use of promethazine HCl

One patient received promethazine HCl for nausea and vomiting, administered transdermally as a pluronic lecithin organogel (PLO) gel in doses ranging from 1-4 mL for up to 24 hours.

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

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

In the study, the author concluded that transdermal PLO promethazine helped relieve severe nausea and vomiting.[7] Refer to Table 5 for summary of authors' conclusions.

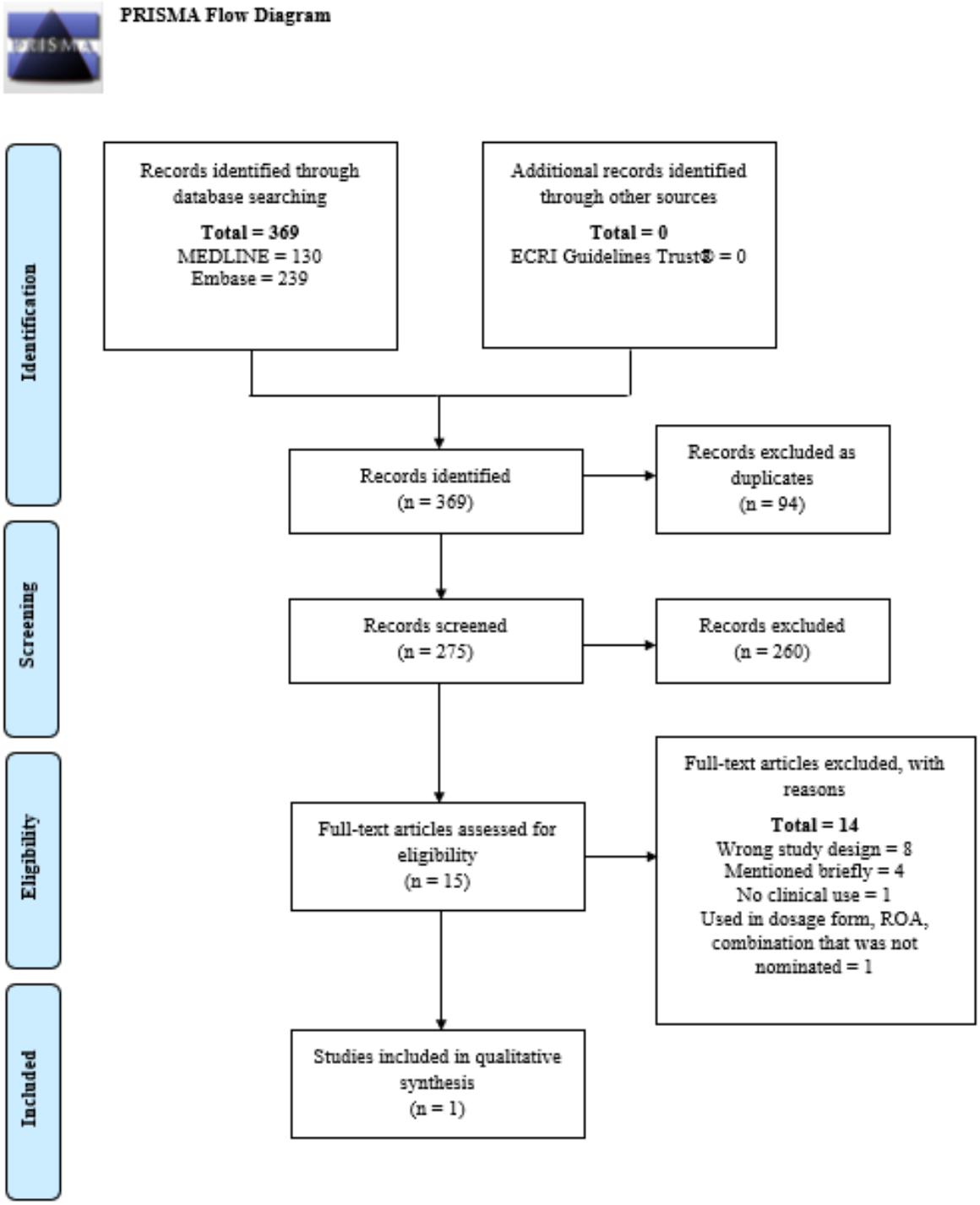
Pharmacology and historical use

In addition to the 1 included study, 1 study was identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of promethazine HCl.

In a 2013 review regarding compounding medications for nausea and vomiting in pregnancy, the author recommended compounded transdermal PLO promethazine as a second-line option.[8] The author listed several advantages of transdermal promethazine.[8] One advantage was reduction in anticholinergic side effects due to less medicine entering the bloodstream, thereby improving patient compliance.[8] Another advantage was for pregnant women who are unable to take oral medications due to severe upper gastrointestinal tract sensitivity during the first trimester, and for whom the rectal route is inconvenient.[8] Based on the author's experience, some women with nausea and vomiting during pregnancy have difficulties swallowing doxylamine and pyridoxine (first-line treatments) even if they come in a small size 2 or 3 capsule, and have no other solution but to be hospitalized for parenteral therapy.[8] These patients would be candidates for transdermal promethazine treatment at the onset of nausea and vomiting, and once there has been sufficient relief, usually within a few days, they can be switched to the oral first-line treatment for long-term prophylactic therapy.[8] For hyperemesis gravidarum, the author recommended transdermal promethazine 12.5 mg three to four times a day in addition to 4 capsules of doxylamine and pyridoxine.[8] The dose of promethazine should be reduced if the patient is experiencing anticholinergic side effects.[8] The case report included

in the literature review used compounded transdermal PLO promethazine to help relieve severe nausea and vomiting in a 9-year old boy who did not want to use the rectal suppository.[7] The author found that transdermal promethazine provided effective relief without major adverse events.[7]

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



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

Table 3. Types of studies

Types of Studies	Number of Studies
Descriptive[7]	1
Experimental	0
Observational	0

Table 4. Number of studies by country

Country	Number of Studies
US[7]	1
	Total US: 1 Total Non-US Countries: 0

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age range)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Muller, 2009, US[7]	Case report	9-year-old male with acute viral gastritis	Transdermal PLO promethazine	Resolution of nausea and vomiting	The compounded transdermal PLO promethazine used was helpful in relieving severe nausea and vomiting in patients who resist other dosage forms or cannot tolerate them.

Abbreviation: PLO, pluronic lecithin organogel.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Nausea/Vomiting[7]	1-4 mL	25 mg/mL	PLO gel	Transdermal	Up to 24 hours

Abbreviation: "–", not mentioned; PLO, pluronic lecithin organogel.

Table 7. Dosage by indication – non-US countries

No studies from non-US countries included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method		Dosage Form	Final Strength
Nausea and vomiting[7]	2009	Promethazine hydrochloride Skin So Soft Pluronic F-127 gel Lecithin/isopropyl palmitate Total 30 mL	0.75 g 10 drops 23 mL 6.6 mL	PLO gel	25 mg/mL

Abbreviation: PLO, pluronic lecithin organogel.

Table 10. Compounded products – non-US countries

No studies from non-US countries 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 promethazine HCl. Amongst these 5 SMEs, there were 5 medical doctors. The SMEs specialized and/or were board-certified in allergy and primary care/family practice, working in academic medical centers and hospital/health systems. The SMEs had been in practice for 14 to 30 years.

Phenergan® (promethazine HCl) is used for motion sickness, hyperemesis, nausea, and vomiting. Several SMEs added promethazine HCl is also given with migraine or pain drugs for the nausea that may accompany the pain. One SME commented that for some migraine patients who get really nauseous, they will use a rectal suppository because the patient might vomit anything taken orally. Another SME stated that promethazine HCl is used more often in pediatric gastrointestinal patients, typically in the emergency room. A few SMEs, including some allergists, mentioned that they do not use promethazine HCl for allergy symptoms. One allergist stated that promethazine HCl has some antihistamine properties that can interfere with results when skin testing for allergies; however, since they do not tell patients to take promethazine HCl, this is not an issue. Another allergist SME did not see a strong need for topical use because they do not usually use topical formulations. They "think of topical steroids or itch-relief compounds [as] outside the antihistamine area."

Several primary care SMEs expressed they could see the nominated topical route being useful. One SME said that while they have not used the topical formulation for pruritis, "it does make a little bit of sense." Another SME stated they have used promethazine HCl topically. Other dosage forms and ROAs the SMEs mentioned that they had used, or heard of other using, included oral liquid, rectal suppositories and intramuscular.

Results of survey

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

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.2 for survey instrument).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. Five respondents (2% of 290 responses, where respondents were allowed to select multiple drug products) obtained promethazine hydrochloride from a 503B outsourcing facility (refer to Table 15).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 16).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which promethazine hydrochloride prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded promethazine hydrochloride

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded promethazine hydrochloride

No respondents to survey distributed via professional medical associations

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	**Responses, n (N=230)**
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	**Responses, n (N=290)[a]**
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31

Epinephrine / Bupivacaine / Fentanyl	3
Fentanyl	10
Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanil	4
Sufentanil	2
Tramadol	2
None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

[a]Survey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	Responses, n (N=686)[a]
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other[b]	40

[a]Survey respondents were allowed to select multiple procedure types.
[b]No respondents provided description for 'Other' procedure type.

CONCLUSION

Promethazine HCl was nominated for inclusion on the 503B Bulks List for allergic rhinitis, hyperemesis gravidarum, motion sickness, nausea and vomiting, nystagmus, postoperative pain, sedation, and pruritus via a 0.5-50 mg/mL topical gel and a 0.5-25 mg/mL intravenous and intramuscular injection. Promethazine HCl is available as a solution for injection in the Abu Dhabi, Australia, New Zealand, US, and UK; it is not available as topical gel in any of the medical registries searched.

From the literature review and interviews conducted, promethazine HCl is used for nausea and vomiting. There has been one US case report published that used promethazine HCl as a PLO gel for nausea and vomiting. Several SMEs stated that promethazine HCl is given with migraine or pain drugs for the nausea that may accompany the pain. A few SMEs, including some allergists, mentioned that they do not use promethazine HCl for allergy symptoms; one allergist SME stated that promethazine HCl has some antihistamine properties that can interfere with results when skin testing for allergies.

For the nominated topical route, several primary care SMEs expressed they could see it being useful; one SME had used promethazine HCl topically. On the other hand, one allergist SME did not see a strong need for topical use.

Zero people responded to the survey distributed via professional medical associations and available on the project website. From the responses to the ASCA survey, 5 respondents (2% of 290 responses, where respondents were allowed to select multiple drug products) obtained promethazine hydrochloride from a 503B outsourcing facility.

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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 26, 2020
- Date last searched: March 29, 2020
- Limits: Humans (search hedge); English language
- Number of results: 130

1	promethazine/	3002
2	proazamin$.tw.	0
3	promazinamid$.tw.	0
4	prometha#in$.tw.	2171
5	prometa#in$.tw.	20
6	or/1-5	3983
7	administration, topical/	38087
8	administration, cutaneous/	21808
9	topical$.tw.	103115
10	percutaneous$.tw.	141677
11	cutaneous$.tw.	148862
12	transcutaneous$.tw.	14158
13	epicutaneous$.tw.	1981
14	transdermal$.tw.	14283
15	derm$.tw.	237716
16	emulsions/	17692
17	exp gels/	50795
18	liniments/	122
19	ointments/	12747
20	skin cream/	983

21	suspensions/	7698
22	emulsion?.tw.	32158
23	gel?.tw.	304210
24	liniment?.tw.	143
25	ointment?.tw.	11664
26	salve?.tw.	338
27	paste?.tw.	12166
28	unguent$.tw.	111
29	lotion?.tw.	2266
30	cream?.tw.	18525
31	suspension?.tw.	106972
32	or/7-31	1103840
33	and/6,32	219
34	exp animals/ not humans/	4683273
35	33 not 34	163
36	limit 35 to english language	130

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 29, 2020
- Limits: Humans (search hedge); English language
- Number of results: 239

1	promethazine'/mj	5847
2	proazamin*':ti,ab,tn	1
3	promazinamid*':ti,ab,tn	1
4	promethacin*':ti,ab,tn	9
5	promethazin*':ti,ab,tn	3707
6	prometacin*':ti,ab,tn	0
7	prometazin*':ti,ab,tn	42
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	7878
9	topical drug administration'/de	81600
10	cutaneous drug administration'/de	619
11	transdermal drug administration'/de	8898
12	topical treatment'/de	12439
13	topical*':ti,ab	146450
14	cutaneous*':ti,ab	213765
15	transcutaneous*':ti,ab	18964
16	epicutaneous*':ti,ab	3357
17	transdermal*':ti,ab	20847
18	dermal*':ti,ab	73061
19	cream'/de	9196
20	gel'/exp	73660
21	liniment'/de	248
22	lotion'/de	2808

23	ointment'/exp	18384
24	paste'/de	2490
25	salve'/de	165
26	emulsion'/exp	44296
27	suspension'/de	26332
28	cream$':ti,ab	29051
29	emulsion$':ti,ab	44001
30	lotion$':ti,ab	3943
31	ointment$':ti,ab	21296
32	paste$':ti,ab	14652
33	salve$':ti,ab	470
34	unguent*':ti,ab	239
35	liniment*':ti,ab	239
36	gel$':ti,ab	357623
37	suspension$':ti,ab	142561
38	#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 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	1115078
39	#8 AND #38	406
40	[animals]/lim NOT [humans]/lim	6010640
41	#39 NOT #40	316
42	#39 NOT #40 AND [english]/lim	239

Appendix 2.1. Survey instrument for professional medical associations

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

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

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

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

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

1. How familiar are you with the following terms?

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

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

   - o Yes
   - o No

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

   - o Topical gel
   - o None of the above

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

   - o Allergic rhinitis
   - o Hyperemesis gravidarum
   - o Motion sickness
   - o Nausea and vomiting
   - o Nystagmus
   - o Pruritus
   - o Sedation for procedure or induction
   - o Other (please describe) _____

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

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

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

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

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

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

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

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

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

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

Appendix 2.2. Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk 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

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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 utilize a 503B outsourcing facility to acquire compounded drugs?

   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

   - o I do not obtain any compounded drugs from 503B outsourcing facilities
   - o Amitriptyline / Ketoprofen / Oxymetazoline
   - o Budesonide
   - o Calcium gluconate
   - o Droperidol
   - o Epinephrine
   - o Epinephrine for ophthalmic administration
   - o Epinephrine / Lidocaine for ophthalmic administration
   - o Epinephrine / Bupivacaine / Fentanyl
   - o Fentanyl
   - o Flurbiprofen
   - o Flurbiprofen for ophthalmic administration
   - o Hydromorphone
   - o Ipamorelin
   - o Ketoprofen / Nifedipine
   - o Lidocaine / Epinephrine / Tetracaine HCl
   - o Meperidine
   - o Morphine
   - o Naloxone
   - o Neomycin
   - o Phentolamine
   - o Promethazine

- o Remifentanil
- o Sufentanil
- o Tramadol
- o None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

    - o Dental
    - o Dermatology
    - o Endoscopy
    - o Neurosurgery
    - o Obstetrics/gynecology
    - o Ophthalmology
    - o Otolaryngology
    - o Orthopedics
    - o Pain
    - o Plastics
    - o Podiatry
    - 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.