Summary Report

Chlorpromazine 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
HCl	Hydrochloride
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 chlorpromazine hydrochloride (chlorpromazine HCl; UNII code: 9WP59609J6), 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 chlorpromazine 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 chlorpromazine 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 chlorpromazine HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Chlorpromazine HCl was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc for nausea, vomiting, confusion, and agitation in hospice patients via a topical gel and 25 mg, 50 mg, and 100 mg rectal suppositories.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of chlorpromazine HCl.[6-10]

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

- Tablets and injections are not appropriate for rectal administration. There are no suppositories commercially available.
- Chlorpromazine suppositories and transdermal gels are typically prescribed to hospice patients who are not able to take many medications by mouth. "Injections are not recommended because of their physiological and mental state."

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of chlorpromazine 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 chlorpromazine HCl; name variations of chlorpromazine 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 chlorpromazine 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 three concepts: chlorpromazine HCl; topical or rectal administration and forms; and therapeutic or preventative use for nausea, vomiting, agitation, or confusion (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 23, 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 23, 2020 for clinical practice guidelines that recommended the use of chlorpromazine 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 chlorpromazine 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 chlorpromazine 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 chlorpromazine 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 chlorpromazine HCl; setting; total number of patients; number of patients who received chlorpromazine HCl; patient population; indication for use of chlorpromazine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of chlorpromazine HCl in a combination product; use and formulation of chlorpromazine HCl in a compounded product; use of chlorpromazine 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 chlorpromazine HCl 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 chlorpromazine HCl: palliative care, primary care and internal medicine, and psychiatry. 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 chlorpromazine 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 persons. 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

- Chlorpromazine HCl is not available as an FDA-approved product in the nominated dosage form and ROA.
- Chlorpromazine 25 mg and 100 mg rectal suppositories have been discontinued, not for safety or efficacy reasons.
- Chlorpromazine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for chlorpromazine HCl.
- Chlorpromazine HCl is not available in the nominated dosage form and ROA in any of the foreign medical registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 580 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 509 titles and abstracts were screened. After screening, the full text of 35 articles was reviewed. Finally, 2 studies were included. Thirty-three studies were excluded for the following reasons: wrong study design (24 studies); chlorpromazine HCl only mentioned briefly (4); duplicate study (3); wrong dosage form or ROA (2).

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

Characteristics of included studies

The 2 included studies were published in 1984 and 1994. There was 1 experimental study, 0 observational studies, 1 descriptive study, and 0 clinical practice guidelines. The 2 studies were conducted in the US.

A total of 43 patients participated in the 2 included studies. The number of patients in each study ranged from 20 to 23.

Outcome measures differed among the included studies and included: level of arousal and degree of restlessness, number of emesis episodes/hour, duration of emesis, and patient preference for emesis regimen.

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

Use of chlorpromazine HCl

Twenty patients received chlorpromazine HCl as a treatment for terminal restlessness and dyspnea, administered either intravenously 13-150 mg/day or rectally 12-300 mg/day. Duration of treatment lasted for a mean of 2 days and ranged from 1 to 5 days. Twenty-three patients received chlorpromazine HCl as a treatment for nausea and vomiting, administered as a rectal suppository in doses ranging from 100 to 400 mg/day.

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

Chlorpromazine HCl was not used as a compounded product, nor was it nominated as a combination product.

In 1 study, the authors' concluding statement recommended the use of chlorpromazine HCl for terminal restlessness and dyspnea in advanced cancer.[11] While in another study, the authors' concluded that droperidol was superior to conventional antiemetics for cisplatinum-related nausea and vomiting.[12] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

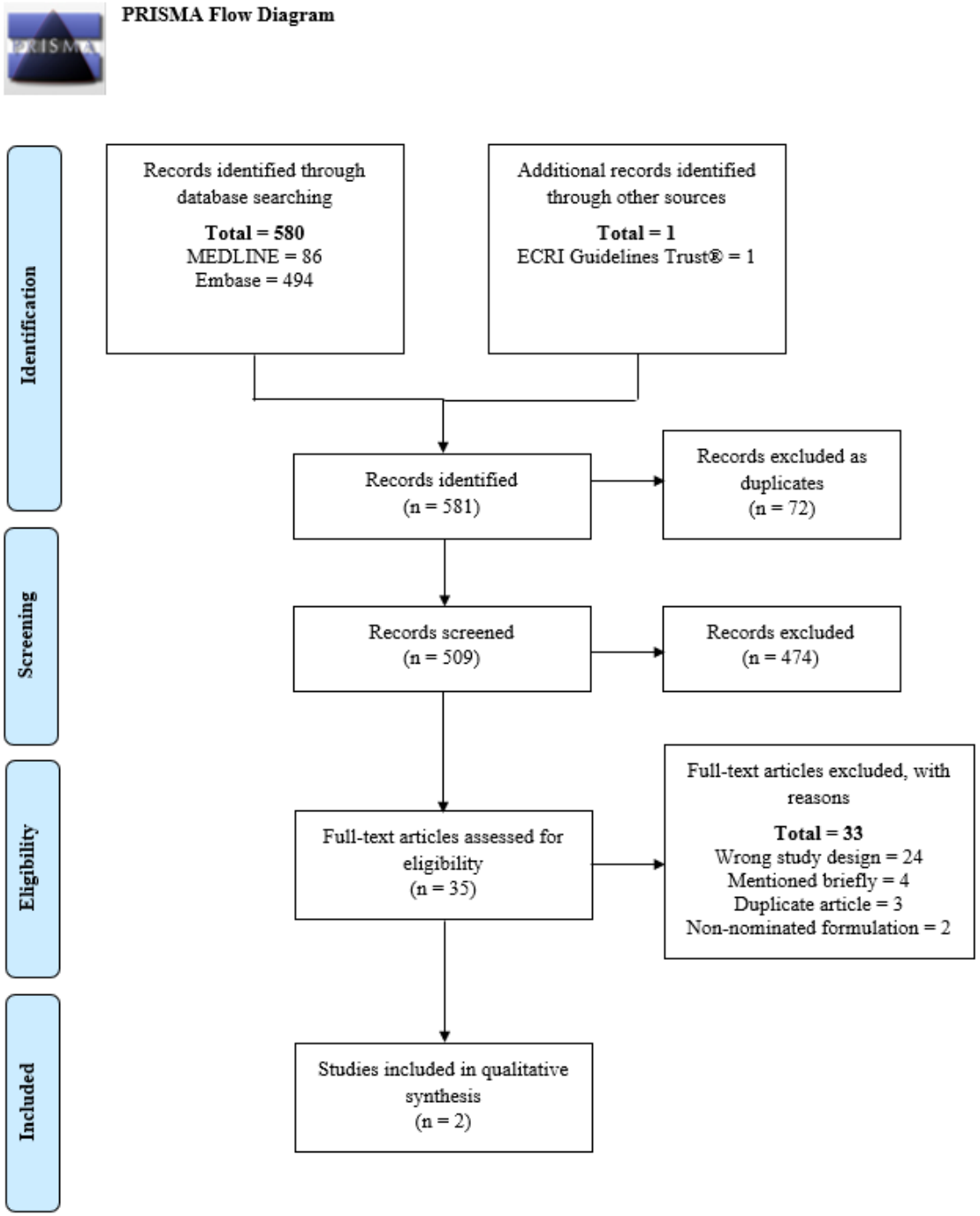
In addition to the 2 included studies, 7 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of chlorpromazine HCl.

Chlorpromazine was first synthesized in 1952 for treatment of psychotic disorders.[11] It is a versatile drug due to being safe even at high doses and the many routes it can be administered.[11] The routes of interest per the nomination are topical gels and rectal suppositories.

From a 2019 review about transdermal delivery of antipsychotics, there was mention of 2 studies looking at the use of pluronic lecithin organogel (PLO) for chlorpromazine transdermal delivery.[13] The first study mentioned showed that the PLO chlorpromazine increased drug permeation through pig and human skin.[13,14] The authors concluded that the PLO gel did not achieve the needed systemic levels of chlorpromazine and that a "chlorpromazine PLO gel may not be effective in treating nausea and vomiting for hospice patients with swallowing difficulties."[14] The other study investigated chlorpromazine PLO gel absorption and found that there was no detectable chlorpromazine concentration in the blood samples of the healthy volunteers. The authors think this is the result of applying the gel to the inner wrist, which is the most commonly used area in hospitals but not the most permeable.[13] Further research for topical formulations of chlorpromazine are still needed to determine proper use and application site.[13]

Chlorpromazine rectal suppositories 25 mg and 100 mg have been discontinued, not for safety or efficacy reasons. Several articles in the literature provided the rectal dosing information. One article reported 50-150 mg every 8 hours rectally for palliative management of patients with intestinal obstruction who have nausea and vomiting.[15] The other articles mentioned chlorpromazine 50-100 mg every 6-8 hours rectally for nausea and vomiting.[16-19] In a prescribing information insert for Largactil® (chlorpromazine HCl) 100 mg suppositories, the rectal route dosing recommended in adults was 100-300 mg daily.[20]

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[11]	1
Experimental[12]	1
Observational	0

Table 4. Number of studies by country

Country	**Number of Studies**
US[11,12]	2
	Total US: 2 Total Non-US Countries: 0

Table 5. Summary of included studies

Indication 1: Nausea and vomiting					
Author, Year, Country	**Study Type[a]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Roberts *et al.*, 1985, US[12]	Randomized	23 patients (0%, range 19-71 y)	• Chlorpromazine and promethazine prior to chemotherapy (23)* *Then each patient randomized to receive chlorpromazine/promethazine or droperidol during chemotherapy. All patients received each regimen at least once.	Number of emesis episodes per hour, duration of emesis, patient preference for either regimen	Droperidol appears to be superior to the more conventional antiemetics for cisplatinum-related nausea and vomiting.
Indication 2: Terminal restlessness and dyspnea					
Author, Year, Country	**Study Type[a]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
McIver *et al.*, 1994, US[11]	Open study	20 inpatients and outpatients (45%, range 16-81 y)	• Chlorpromazine intravenously (10) • Chlorpromazine rectally (10)	Level of arousal and degree of restlessness within 24 hours of initial order and every 24 hours until death	Chlorpromazine is a safe and effective drug and is a first-line agent for treatment of terminal restlessness and dyspnea in advanced cancer. Rectal administration was as effective as intravenous administration for this indication.

Abbreviation: "–", not mentioned.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Nausea and vomiting[12]	100-400 mg/day	–	Suppository	Rectal	–
Terminal restlessness and dyspnea[11]	13-150 mg/day	–	–	Intravenous	Until death (mean of 2 days, range 1-5 days)
	12-300 mg/day	–	–	Rectal	

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No studies from non-US countries

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

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. Ten SMEs discussed chlorpromazine. Amongst the 10 SMEs, there were 6 medical doctors, 3 pharmacists, and 1 nurse practitioner. The SMEs specialized and/or were board-certified in child and adolescent psychiatry, internal medicine, geriatrics, oncology/hematology, palliative care, pharmacotherapy, psychiatry, and primary care/family practice, working in academia, academic medical centers, and private practice/clinics. The SMEs had been in practice for 6 to 34 years.

Thorazine® (chlorpromazine) used to be marketed and was a branded product, making it very expensive. Chlorpromazine was effective for agitation in the elderly and/or end of life care and agitated delirium in people who were at a risk of harming themselves and others. It is sedating and a "good drug for that niched purpose." However, chlorpromazine is usually not the first go-to and has largely been replaced by Zofran® (ondansetron) or Haldol® (haloperidol). One SME commented that "nobody is using it anymore." There is a new generation of atypical antipsychotics with less side effects. However, sometimes when there are "atypical issues," one might go back to using chlorpromazine. On the other hand, one SME specializing in psychiatry commented that chlorpromazine is still used a lot PRN in acute care settings such as residential treatment programs, inpatient units, and the emergency room. Another SME stated that chlorpromazine suppositories were used in psychiatric facilities in the past, but they do not give rectal products at these facilities anymore. Chlorpromazine is also used in kids if a more serious PRN medication is needed in the inpatient setting for acute agitation. One SME also mentioned using chlorpromazine for hiccups.

The SMEs had differing views on the nominated dosage forms and ROA. Several SMEs would like chlorpromazine available as a topical gel. A topical gel is easier to apply to an agitated patient, instead of making the patient take a pill. Topical would also be a good alternative to giving a kid a shot. One SME specializing in oncology remarked that if a topical gel worked, it would be fabulous. They do not have anything topical except for scopolamine and Compazine® (prochlorperazine) patches. Oral is the typical route of administration, administering the liquid form via the percutaneous endoscopic gastrostomy (PEG) tube. Another SME said they could make sense of the topical gel used for hospice patients, but

after other drugs have failed. On the other hand, several SMEs were either unsure if the topical formulation had any absorption or commented that a topical formulation would not work. One SME stated they would never use a compounded topical application on intact skin because it does not work and would only have a placebo effect (makes the nurse feel better). Another SME also added that the topical route might not be good for agitation because of the "time to rub in and more people over the bed," which "might make sense for palliative care [as] touch might be good."

Similarly, there were mixed thoughts on the rectal dosage form. One SME expressed being tempted to use the 100 mg rectal suppository in an agitated delirium patient, and it would be nice to have other dosage strengths available. The rectal route would work quicker than the topical route. Another SME also added that rectal agents may be used in hospice patients because they may not be able to swallow anything. In contrast, several SMEs stated they would not use the rectal dosage form. One SME who specializes in oncology commented they are not a fan of suppositories because many of their patients have issues with platelets or white blood cells. Another SME stated that the rectal route is not good for agitation in kids and in general, psychiatric conditions; for delirium, IV is the best way to go. One SME also commented that "in psychiatry, I can't imagine a reason for giving rectal medications." There might be other uses for chlorpromazine outside of psychiatry where it might make sense. Besides the nominated dosage forms and ROA, one SME also commented that it would be nice to have a high concentrated oral solution. Another SME would only refill chlorpromazine if a psychiatrist started the patient on it.

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 chlorpromazine prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded chlorpromazine

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded chlorpromazine

No respondents to survey distributed via professional medical associations

CONCLUSION

Chlorpromazine HCl was nominated for inclusion on the 503B Bulks List for nausea, vomiting, confusion, and agitation in hospice patients via a topical gel and 25 mg, 50 mg, and 100 mg rectal suppositories. Chlorpromazine 25 mg and 100 mg rectal suppositories have been discontinued, not for safety or efficacy reasons. Additionally, chlorpromazine HCl is not available in any of the national medical registries searched.

From the literature review and interviews conducted, chlorpromazine was used in agitation in the elderly, delirium, hiccups, nausea and vomiting, and terminal restlessness and dyspnea. In the articles included for the literature review, chlorpromazine was used rectally. As for the topical formulation, a review looking at the use of transdermal delivery of antipsychotics mentioned 2 studies that explored PLO chlorpromazine absorption. Both studies did not achieve good absorption and further research for topical formulations of chlorpromazine are still needed.

The SMEs had mixed views for both the topical gel and rectal suppositories. Several SMEs would like a topical gel available due to ease of application in patients and expanding available topical options. Other SMEs disagreed due to how long topical formulations would take before working for agitation, potential absorption issues, and topical applications not working on intact skin. For the rectal suppositories, some SMEs would like to use this formulation in agitated delirium and hospice patients. In contrast, others stated they prefer to not use suppositories in specific patient populations such as patients with platelet or white blood cell issues or patients with psychiatric conditions.

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 20, 2020
- Date last searched: March 23, 2020
- Limits: Humans (search hedge); English language
- Number of results: 86

1	chlorpromazine/	17220
2	chlorproma#in$.tw.	12368
3	chlorbroma#in$.tw.	3
4	chloroproma#in$.tw.	213
5	chlorpromanyl$.tw.	0
6	clorproma#in$.tw.	10
7	klorproma#in$.tw.	0
8	or/1-7	21170
9	administration, topical/	38076
10	administration, cutaneous/	21801
11	administration, rectal/	2514
12	administration, mucosal/	251
13	topical$.tw.	103032
14	cutaneous$.tw.	148769
15	percutaneous$.tw.	141577
16	transdermal$.tw.	14272
17	mucosal$.tw.	118037
18	rectal$.tw.	86582
19	gels/	28600
20	suppositories/	3917

21	gel?.tw.	304100
22	suppositor$.tw.	4364
23	or/9-22	915583
24	drug therapy/	30382
25	exp nausea/	19612
26	exp vomiting/	30938
27	exp confusion/	13627
28	palliative care/	53120
29	exp terminal care/	50569
30	dt.fs.	2188594
31	ad.fs.	1395913
32	tu.fs.	2194831
33	pc.fs.	1266387
34	therap$.tw.	2713908
35	treat$.tw.	5373014
36	prevent$.tw.	1383876
37	prophyla$.tw.	161554
38	nause$.tw.	59445
39	vomit$.tw.	68002
40	emesis.tw.	6565
41	agitat$.tw.	19537
42	confusion$.tw.	34230
43	deli?r$.tw.	15304
44	palliat$.tw.	73305
45	hospice$.tw.	12133
46	((end or terminal$) adj2 care).tw.	3151

47	or/24-46	9572295
48	and/8,23,47	192
49	exp animals/ not humans/	4680951
50	48 not 49	99
51	limit 50 to english language	86

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 23, 2020
- Limits: Humans (search hedge); English language
- Number of results: 494

1	chlorpromazine'/de	53276
2	chlorpromazin*':ti,ab,tn	19290
3	chlorpromasin*':ti,ab,tn	17
4	chlorbromazin*':ti,ab,tn	0
5	chlorbromasin*':ti,ab,tn	0
6	chloropromazin*':ti,ab,tn	297
7	chloropromasin*':ti,ab,tn	1
8	chlorpromanyl*':ti,ab,tn	2
9	clorpromazin*':ti,ab,tn	38
10	clorpromasin*':ti,ab,tn	0
11	klorpromazin*':ti,ab,tn	1
12	klorpromasin*':ti,ab,tn	0
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	33609
14	rectal drug administration'/de	8655
15	topical drug administration'/de	81516
16	cutaneous drug administration'/de	618
17	mucosal drug administration'/de	416
18	transdermal drug administration'/de	8877
19	topical*':ti,ab	146246
20	cutaneous*':ti,ab	213485
21	transdermal*':ti,ab	20809
22	percutaneous*':ti,ab	216361

23	mucosal*':ti,ab	167892
24	rectal*':ti,ab	137034
25	gel'/exp	73453
26	suppository'/de	6012
27	gel$':ti,ab	357343
28	suppositor*':ti,ab	7073
29	#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	1304124
30	drug therapy'/de	712920
31	add on therapy'/de	18546
32	drug dose':lnk	622119
33	drug administration':lnk	1721606
34	drug therapy':lnk	3850278
35	prevention':lnk	1161039
36	nausea and vomiting'/exp	366198
37	confusion'/exp	30248
38	delirium'/exp	32190
39	agitation'/de	27375
40	terminal care'/exp	68282
41	palliative therapy'/de	88703
42	therap*':ti,ab	4082379
43	treat*':ti,ab	7782581
44	prevent*':ti,ab	1880319
45	prophyla*':ti,ab	257706
46	nause*':ti,ab	110380
47	vomit*':ti,ab	121257
48	emesis':ti,ab	10786

49	agitat*':ti,ab	32293
50	confusion*':ti,ab	53252
51	deli$r*':ti,ab	25629
52	palliat*':ti,ab	120029
53	hospice*':ti,ab	19387
54	((end OR terminal*) NEAR/2 care):ti,ab	4411
55	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54	13267274
56	#13 AND #29 AND #55	794
57	[animals]/lim NOT [humans]/lim	6006575
58	#56 NOT #57	625
59	#56 NOT #57 AND [english]/lim	494

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded chlorpromazine 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 chlorpromazine hydrochloride to your patients?

    - o Yes
    - o No

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

    - o Rectal suppository
    - o Topical gel
    - o None of the above

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

    - o Agitation
    - o Confusion
    - o Nausea and vomiting
    - o Other (please explain) _____

5. I use compounded chlorpromazine 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 chlorpromazine hydrochloride.
    - o Other (please explain) _____

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

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

7. I obtain compounded chlorpromazine 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 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.