Summary Report

Brompheniramine maleate

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
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of brompheniramine maleate (UNII code: IXA7C9ZN03), 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 brompheniramine maleate 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 brompheniramine maleate 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 brompheniramine maleate 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

Brompheniramine maleate was nominated for inclusion on the 503B Bulks List by Specialty Sterile Pharmaceutical Society (SSPS) and US Compounding Pharmacy.

Brompheniramine maleate was nominated for the treatment of allergic rhinitis, urticarial transfusion reaction, urticaria, vasomotor rhinitis, and as an adjunct for anaphylaxis via a 10 mg/mL intramuscular (IM) preserved solution.

The nominators did not provide references from published peer-reviewed literature to describe the pharmacology and support the clinical use of brompheniramine maleate.

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

- Prescriber or hospital preference for various strengths, 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.
- Brompheniramine has been discontinued. However, it is sometimes preferred by practitioners over available alternatives such as hydroxyzine and diphenhydramine based on efficacy studies and published adverse event profiles.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of brompheniramine maleate 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 brompheniramine maleate; name variations of brompheniramine maleate 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 brompheniramine maleate. 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

Brompheniramine maleate is a component of an FDA-approved product that was discontinued by the manufacturer, not for safety or efficacy reasons. The nominated compounded products did not differ substantially from the commercially available product. Therefore, a systematic literature review was not conducted.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances brompheniramine maleate was used in a clinical setting. The indications from the nominations were reviewed to identify the following medical specialties that would potentially use brompheniramine maleate: allergy and immunology, emergency medicine and critical care, and primary care and internal medicine. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those

codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of brompheniramine maleate 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

- Brompheniramine maleate is not available as an FDA-approved product in the nominated dosage form and ROA.
- Brompheniramine maleate 10 mg/mL and 100 mg/mL injections have been discontinued, not for reasons of safety or efficacy.
- Brompheniramine maleate is available in various oral dosage forms as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for brompheniramine maleate.
- Brompheniramine maleate is not available in the nominated dosage form and ROA in any of the foreign medicine 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

No literature review was conducted.

Pharmacology and historical use

No additional references were found that provided information about the pharmacological or historical use of brompheniramine maleate.

Table 3. Types of studies

No literature review was conducted.

Table 4. Number of studies by country

No literature review was conducted.

Table 5. Summary of included studies

No literature review was conducted.

Table 6. Dosage by indication – US

No literature review was conducted.

Table 7. Dosage by indication – non-US countries

No literature review was conducted.

Table 8. Number of studies by combination

No literature review was conducted.

Table 9. Compounded products – US

No literature review was conducted.

Table 10. Compounded products – non-US countries

No literature review was conducted.

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. Seven SMEs discussed brompheniramine. Amongst these 7 SMEs, there were 5 medical doctors and 2 pharmacists. The SMEs specialized and/or were board-certified in allergy, critical care pharmacy, pharmacotherapy, primary care and family practice, working in academic medical centers. The SMEs had been in practice for 6 to 30 years.

Although the SMEs often discussed brompheniramine and chlorpheniramine together due to their similarities, these two substances were not nominated for use in combination.

Brompheniramine and chlorpheniramine are old first-generation antihistamines that came before newer ones like Zyrtec® (cetirizine) and other OTC medications. Today's OTC allergy medications are more expensive but have fewer side effects and do not make people drowsy like brompheniramine and chlorpheniramine. One SME expressed that brompheniramine is used in many OTC children's allergy formulations but are not given any more to children less than 6 years old because they do not work and do more harm than good.

Benadryl® (diphenhydramine) and the other second-generation antihistamines are the standard of care for allergy symptoms. For anaphylaxis, the standard therapy is EpiPen® (epinephrine). In the emergency room and the intensive care unit, IV or IM diphenhydramine is used and works well.

None of the SMEs have used brompheniramine or chlorpheniramine injection. One SME's colleague used them many years ago but did not recall their experience with them. Hydroxyzine and diphenhydramine injection are used more commonly, and most SMEs expressed that there is not a need for another agent.

There is a potential use for compounding the oral solution of chlorpheniramine or brompheniramine to give to young children. Children can take liquids easier and the solution could be mixed with other medications like Tylenol® (acetaminophen) if needed. The drowsiness effect could be useful if a child with an earache gets fussy and is up all night screaming.

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 survey respondents provided this information

Table 12. Conditions for which brompheniramine maleate prescribed or administered

No survey respondents provided this information

Table 13. Reasons for using compounded brompheniramine maleate

No survey respondents provided this information

Table 14. Use of non-patient-specific compounded brompheniramine maleate

No survey respondents provided this information

CONCLUSION

Brompheniramine maleate was nominated for inclusion on the 503B Bulks List for treatment of allergic rhinitis, urticarial transfusion reaction, urticaria, vasomotor rhinitis, and as an adjunct for anaphylaxis via a 10 mg/mL IM preserved solution. Brompheniramine maleate is not approved in the nominated dosage form or ROA in any of the national medical registries searched. Brompheniramine maleate 10 mg/mL and 100 mg/mL injections used to be available as FDA-approved products but have been discontinued, not for reasons of safety or efficacy.

From the interviews conducted, brompheniramine maleate is an older first-generation antihistamine. Today's OTC allergy medications are more expensive but have fewer side effects and less drowsiness compared to brompheniramine. None of the SMEs had used brompheniramine injection. Hydroxyzine and diphenhydramine injection are used more commonly, and most SMEs expressed that there is not a need for another agent.

No literature review was conducted, and no survey responses were received.

REFERENCES

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4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

No literature review was conducted.

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded brompheniramine maleate. 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 brompheniramine maleate to your patients?

    - o Yes
    - o No

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

    - o Solution for intramuscular injection
    - o None of the above

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

    - o Allergic rhinitis
    - o Anaphylaxis
    - o Urticaria
    - o Urticarial transfusion reaction
    - o Vasomotor rhinitis
    - o Other (please explain) _____

5. I use compounded brompheniramine maleate 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 brompheniramine maleate.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded brompheniramine maleate at your practice?

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

7. I obtain compounded brompheniramine maleate 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.