Summary Report

# Tromethamine

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

Prepared by:

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

January 2020

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

# Table of Contents

REVIEW OF NOMINATION ..... 4
METHODOLOGY ..... 4
Background information ..... 4
Systematic literature review ..... 5
Outreach to medical specialists and specialty organizations ..... 5
Survey ..... 5
CURRENT AND HISTORIC USE ..... 6
Summary of background information ..... 6
Summary of literature review ..... 6
Summary of focus groups/interviews of medical experts and specialty organizations ..... 7
Summary of survey results ..... 7
CONCLUSION ..... 8
APPENDICES ..... 9
Appendix 1. References ..... 9
Appendix 2. Survey instrument ..... 10

# Table of Tables

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

## REVIEW OF NOMINATION

Tromethamine (UNII code: 383V75M34E) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society to correct metabolic acidosis due to cardiac surgery via a 36mg/mL intravenous solution.

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

- Prescribers' preference for varying concentrations, volumes, or final product container for administration.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is safer and more efficient.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state-of-the-art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.

## METHODOLOGY

### *Background information*

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

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing tromethamine. 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*

Tromethamine is a component of an FDA-approved product that has been discontinued by the manufacturer, not for safety or efficacy reasons. The desired compounded products identified in the submitted nominations do not substantially differ from the commercially available product. Therefore, a systematic literature review was not completed.

*Outreach to medical specialists and specialty organizations*

Using the indication from the nomination and the results of the literature review, two (2) medical specialties that would potentially use tromethamine were identified: cardiology and surgery. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. No interviews were conducted.

*Survey*

General professional medical associations and specialty associations for cardiology and surgery, identified from the nomination was contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to three (3) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

*No associations replied stating they would distribute the survey to their membership*

Table 2. Associations that declined participation

| Specialty | Association | Reasons for Declining |
|---|---|---|
| Medicine | American Medical Association (AMA) | Failed to respond |
| | American Osteopathic Association (AOA) | Failed to respond |
| Surgery | American College of Surgeons (ACS) | Failed to respond |

## CURRENT AND HISTORIC USE

*Summary of background information*

- Tromethamine is not available as an FDA-approved product. Tromethamine was available under the trade name Tham as a 3.6g/100mL solution for injection; however, this product has been discontinued.
- Tromethamine is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for tromethamine.
- Tromethamine is available in Abu Dhabi.

Table 3. Currently approved products – US

*No approved products in the US*

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

| Active Ingredient | Concentration | Dosage Form | ROA | Approved For Use | | |
|---|---|---|---|---|---|---|
| | | | | Country | Status | Approval Date |
| Tromethamine | 360mg/mL, 0.3 molar | Injection | – | Abu Dhabi | Active | – |

Abbreviations: "–", not mentioned; ROA, route of administration.
[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, route of administration and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or routes of administration similar to those requested in the nominations. See Methodology for full explanation.

*Summary of literature review*

No literature review was conducted.

Table 5. Types of studies

*No literature review was conducted*

Table 6. Number of studies by country

*No literature review was conducted*

Table 7. Number of studies by combinations

*No literature review was conducted*

Table 8. Dosage by indication – US

*No literature review was conducted*

Table 9. Dosage by indication – non-US countries

*No literature review was conducted*

Table 10. Compounded products – US

*No literature review was conducted*

Table 11. Compounded products – non-US countries

*No literature review was conducted*

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

Zero (0) interviews were conducted.

Table 12. Overview of interviewee

*No interviews were conducted*

*Summary of survey results*

Table 13. Characteristics of survey respondents [1 person responded to the survey]

| Board Certification | PhD | No response |
|---|---|---|
| No Board certification | 1 | 0 |
| No response | 0 | 0 |

Abbreviation: PhD, Doctor of Philosophy.

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

*No survey respondents provided this information*

Table 15. Compounded use of tromethamine in practice

*No survey respondents provided this information*

Table 16. Indications for which tromethamine is considered a standard therapy

*No survey respondents provided this information*

Table 17. Reasons for using compounded product instead of the FDA-approved products

*No survey respondents provided this information*

Table 18. Change in frequency of compounded tromethamine usage over the past 5 years

*No survey respondents provided this information*

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

*No survey respondents provided this information*

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

*No survey respondents provided this information*

## CONCLUSION

Tromethamine (UNII code: 383V75M34E) was nominated for inclusion on the 503B Bulks List by Specialty Sterile Pharmaceutical Society for the correction of metabolic acidosis due to cardiac surgery. The nominated ROA and dosage form is an intravenous solution for injection. Tromethamine was available as a 3.6g/100mL intravenous solution for injection in the US, but this product has been discontinued. Tromethamine is available in Abu Dhabi.

No literature review or interviews were conducted. From the survey responses, the one (1) respondent did not report use of tromethamine in practice.

## APPENDICES

*Appendix 1. References*

No literature review was conducted.

*Appendix 2. Survey instrument*

**Start of Block: Welcome Page**

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **tromethamine**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

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

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

**End of Block: Welcome Page**

---

**Start of Block: Tromethamine**

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **tromethamine**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☐ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ☐ Unsure

*Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for tromethamine? Please check all th... != Compounded drug product*

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

---

*Display This Question:*

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

Q2. Please list any conditions or diseases for which you use compounded **tromethamine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

| | Strength(s) (please include units) | Dosing frequency(ies) | Dosage form(s) | Route(s) of administration | Duration of therapy | Patient population |
|---|---|---|---|---|---|---|
| Condition 1 (please describe) | | | | | | |
| Condition 2 (please describe) | | | | | | |
| Condition 3 (please describe) | | | | | | |
| Condition 4 (please describe) | | | | | | |
| Condition 5 (please describe) | | | | | | |

Q3. Do you use compounded **tromethamine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

*Skip To: Q5 If Do you use compounded tromethamine as a single agent active ingredient, or as one active ingredient... != Combination*

*Display This Question:*

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

Q4. Please list all combination products in which you use compounded **tromethamine**.

_____

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

_____

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

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **tromethamine** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why) _____
- ○ Yes - I use it **LESS** often now (briefly describe why) _____

- No - use has remained consistent

Q8. Why do you use compounded **tromethamine** instead of any FDA-approved drug product?

_____

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

- Yes
- No

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

*Display This Question:*

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

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

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **tromethamine**? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **tromethamine**? Please check all that apply.

- ☐ Convenience
- ☐ Emergencies
- ☐ Other (please describe) _____

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

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

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

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

_____

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

_____

**End of Block: Tromethamine**

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ☐ Doctor of Medicine (MD)
- ☐ Doctor of Osteopathic Medicine (DO)
- ☐ Doctor of Medicine in Dentistry (DMD/DDS)
- ☐ Naturopathic Doctor (ND)
- ☐ Nurse Practitioner (NP)
- ☐ Physician Assistant (PA)
- ☐ Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ☐ No Board certification
- ☐ Allergy and Immunology
- ☐ Anesthesiology
- ☐ Cardiovascular Disease
- ☐ Critical Care Medicine
- ☐ Dermatology
- ☐ Emergency Medicine
- ☐ Endocrinology, Diabetes and Metabolism
- ☐ Family Medicine
- ☐ Gastroenterology
- ☐ Hematology
- ☐ Infectious Disease
- ☐ Internal Medicine
- ☐ Medical Toxicology
- ☐ Naturopathic Doctor
- ☐ Naturopathic Physician
- ☐ Nephrology
- ☐ Neurology
- ☐ Obstetrics and Gynecology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Otolaryngology
- ☐ Pain Medicine
- ☐ Pediatrics
- ☐ Psychiatry
- ☐ Rheumatology
- ☐ Sleep Medicine
- ☐ Surgery (please describe) _____
- ☐ Urology
- ☐ Other (please describe) _____

End of Block: Background Information