Summary Report

Sodium L-Aspartate Monohydrate

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Prepared by:

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REVIEW OF NOMINATION

Sodium L-aspartate monohydrate (UNII code: 4685ARH0AF) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society for use in bypass surgery as part of the cardioplegia solution. The dose will be customized based on the specifications of the client and administered via an intracardiac injection. The nomination identified the need for combination products. However, no information was provided regarding the specific combination desired.

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

- Prescribers and all hospital formularies have different preferences or requirements for 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 more safe and 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 sodium L-aspartate monohydrate 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 sodium L-aspartate monohydrate; name variations of sodium L-aspartate monohydrate 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 sodium L-aspartate monohydrate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

Two databases (PubMed and Embase) were searched including any date through March 26, 2019. The search included a combination of ("sodium l-aspartate monohydrate"[TIAB] OR "sodium aspartate"[TIAB] OR "sodium aspartate monohydrate"[TIAB] OR "l-aspartate"[TIAB] OR "aspartate sodium"[TIAB]) AND (cardio*[TIAB] OR surgery[TIAB] OR bypass[TIAB] OR treat*[TIAB] OR clinical[TIAB] OR therap*[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of sodium L-aspartate monohydrate or the implementation of sodium L-aspartate monohydrate in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

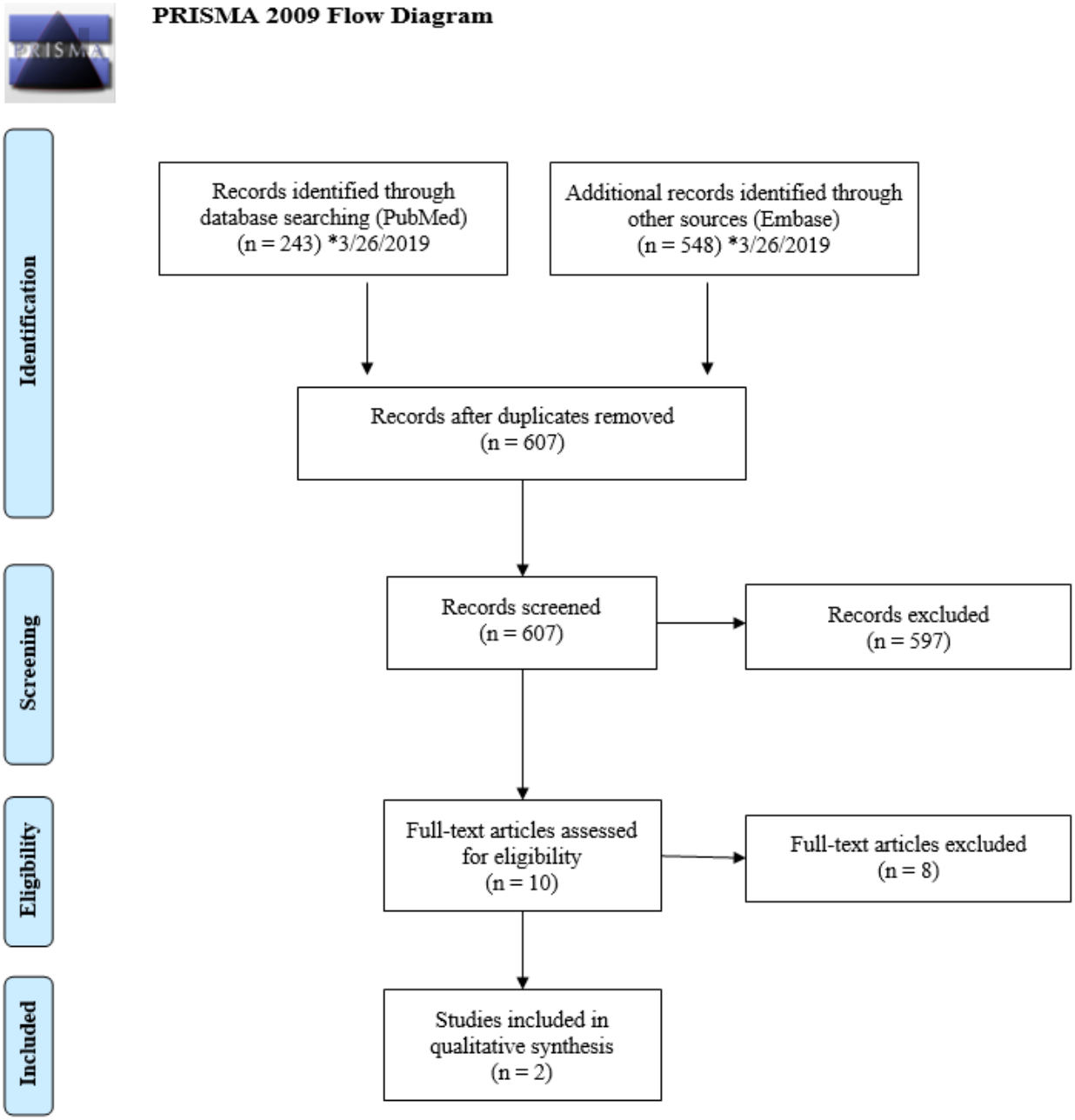
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for sodium L-aspartate monohydrate use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of sodium L-aspartate monohydrate compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indication from the nomination and the results of the literature review, two (2) medical specialties that would potentially use sodium L-aspartate monohydrate were identified: cardiology and surgery. No interviews were conducted.

Survey

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

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to 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 participated

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

- Sodium L-aspartate monohydrate is not available as an FDA-approved product. Injectable amino acids combination prescription products are available, but the specific amino acids in the products are not provided.
- Sodium L-aspartate monohydrate is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for sodium L-aspartate monohydrate.
- Sodium L-aspartate monohydrate is available in Canada and the UK. L-aspartic acid is available in Canada and the UK as a multiple amino acid product as a liquid, emulsion, or solution for intravenous administration.

Table 3. Currently approved products – US

Injectable amino acids combination prescription products are available, but the specific amino acids in the products is not provided.

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

L-aspartic acid is available in Canada and the UK as a multiple amino acid product as a liquid, emulsion, or solution for intravenous administration.

Summary of literature review

- Total number of studies included: two (2) experimental.
- All of the studies were from Turkey (2).
- The only indication for sodium L-aspartate monohydrate was coronary artery bypass grafting (CABG) surgery.
- No compounded products were identified from any of the studies.

Table 5. Types of studies

Types of Articles	Number of Studies
Descriptive	0
Experimental[1,2]	2
Observational	0

Table 6. Number of studies by country

Country	Number of Studies
Turkey[1,2]	2
	Total US: 0 Total Non-US Countries: 2

Table 7. Number of studies by combinations

The nomination identified the need for combination products. However, no information was provided regarding the specific combination desired.

Table 8. Dosage by indication – US

No US studies identified

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Coronary Artery Bypass Grafting (CABG) Surgery[1,2]	10-15mL/kg	13mmol/L	Solution	–	–

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

Table 10. Compounded products – US

No compounded products from reported studies

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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

No interviews were conducted.

Table 12. Overview of interviewees

No interviews were conducted

Summary of survey results

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

Board Certification	PhD
No Board Certification	1

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 sodium L-aspartate monohydrate in practice

No survey respondents provided this information

Table 16. Indications for which sodium L-aspartate monohydrate 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 usage of compounded sodium L-aspartate monohydrate over the past 5 years

No survey respondents provided this information

Table 19. Stocking of non-patient specific compounded sodium L-aspartate monohydrate

No survey respondents provided this information

Table 20. Reasons for stocking non-patient specific compounded sodium L-aspartate monohydrate

No survey respondents provided this information

CONCLUSION

Sodium L-aspartate monohydrate (UNII code: 4685ARH0AF) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society for use in bypass surgery as part of the cardioplegia solution. The dose will be customized based on the specifications of the client and administered via an intracardiac injection. Sodium L-aspartate monohydrate is available in Canada and the UK.

From the literature review conducted, there were two (2) experimental, non-US studies found for use in CABG surgery. No compounded products were identified from any of the studies.

No interviews were conducted. The only survey respondent did not use sodium L-asparate monohydrate.

APPENDICES

Appendix 1. References

1. Doğan ÖF, Duman Ü, Khalil E, Kara KA. Aminoacid enriched cardioplegia decreased the amount of İntramyocardial leucocytes in coronary artery bypass grafting surgery. *Am J Cardiol*. 2018;121(8):e27.
2. Uyar I, Mansuroğlu D, Kirali K, et al. Aspartate and glutamate-enriched cardioplegia in left ventricular dysfunction. *J Card Surg*. 2005;20(4):337-344.

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 **sodium L-aspartate monohydrate**. 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: Sodium L-aspartate monohydrate

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

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

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Display This Question:

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

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

Display This Question:

If Loop current: Do you use compounded sodium L-aspartate monohydrate as a single agent active ingredient, or as one active ingredient... = Combination

Q4. Please list all combination products in which you use compounded **sodium L-aspartate monohydrate**.

_____

Q5. For which, if any, diseases or conditions do you consider compounded **sodium L-aspartate monohydrate** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **sodium L-aspartate monohydrate** in medical practice guidelines or other resources?

_____

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

_____

Q9. Do you stock non-patient-specific compounded **sodium L-aspartate monohydrate** in your practice location?

- Yes
- No

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

Display This Question:

If Do you stock non-patient-specific compounded sodium L-aspartate monohydrate in your practice location? = Yes

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

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

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

Q13. For which, if any, diseases or conditions do you consider **sodium L-aspartate monohydrate** standard therapy?

_____

Q14. Does your specialty describe the use of **sodium L-aspartate monohydrate** in medical practice guidelines or other resources?

_____

End of Block: Sodium L-aspartate monohydrate

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