Summary Report

Magnesium chloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946

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December 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.

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
TPN	Total parenteral nutrition
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 magnesium chloride (UNII code: 02F3473H9O), 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 magnesium chloride 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 magnesium chloride 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 magnesium chloride 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

Magnesium chloride was nominated for inclusion on the 503B Bulks List by the Alliance of Natural Health USA (ANH-USA), the American Association of Naturopathic Physicians (AANP), David Smith, the Integrative Medical Consortium, and McGuff Compound Pharmacy Services. Magnesium chloride was nominated for use in combination with calcium gluconate, sodium ascorbate, and vitamin B complex.

Magnesium chloride was nominated for electrolyte supplementation via intravenous administration of a 200 mg/mL injection as a multi-dose or preservative-free product.

Magnesium chloride was nominated for vitamin deficiency via an intramuscular injection in combination with vitamin B complex, vitamin C (sodium ascorbate), and calcium gluconate.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of magnesium chloride.[6-13]

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

- There is no FDA-approved magnesium chloride injection that is available as a single drug product.
- There is no FDA-approved injectable drug product that contains magnesium chloride in combination with vitamin B complex, vitamin C (sodium ascorbate), and calcium gluconate
- Compounding from the bulk product would improve the accuracy of the final product compared to using the commercial product.
- While there may be commercially available FDA-approved medications containing the active ingredient being prescribed, the dosage form, strength or flavor of the manufactured product may be inappropriate for the patient.
- Commercially available medications may contain excipients such as fillers and preservatives that cannot be tolerated by the patient because of sensitivities or allergies to these substances.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of magnesium chloride 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 magnesium chloride; name variations of magnesium chloride 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 magnesium chloride. 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 constructed for another nominated substance, sodium ascorbate, were used because magnesium chloride was nominated for use in combination with this substance via the same ROA. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: sodium ascorbate, intravenous or intramuscular administration, and therapeutic use (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 4, 2020. Separate search strategies for studies on the use of intravenous magnesium chloride alone were not conducted because magnesium chloride injection (200 mg/mL) has been marketed in the US since pre-1938 and is currently available as a "grandfathered" drug product. There have been no recalls of the product due to safety or efficacy reasons. In addition, the ECRI Guidelines Trust® repository was searched on March 4, 2020 for clinical practice guidelines that recommended the use of magnesium chloride and provided sufficient information on dosing and administration. The reference lists of clinical practice guidelines were reviewed to identify additional studies.

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 magnesium chloride 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 magnesium chloride 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 magnesium chloride 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 magnesium chloride; setting; total number of patients; number of patients who received magnesium chloride; patient population; indication for use of magnesium chloride; dosage form and strength; dose; ROA; frequency and duration of therapy; use of magnesium chloride in a combination product; use and formulation of magnesium chloride in a compounded product; use of magnesium chloride 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 magnesium chloride was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use magnesium chloride: naturopathy, nutrition, 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 magnesium chloride in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Magnesium chloride is not available as an FDA-approved product in the nominated combination. It is available as an unapproved drug as a 200 mg/mL solution for intravenous injection, as well as several injectable combination products.
- Magnesium chloride is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for magnesium chloride.
- Magnesium chloride is available in the nominated dosage form and ROA in Belgium and Canada.

Table 1. Currently approved products – US

No approved products in the US

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date
Magnesium chloride	0.51-100 g/L	Solution	Dialysis, intravenous	Belgium	Medical prescription	02/08/2004
				Canada	Ethical	12/31/1993

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

Results of literature review

Study selection

Separate search strategies for studies on the use of intravenous magnesium chloride alone were not conducted because magnesium chloride injection (200 mg/mL) has been marketed in the US since pre-1938 and is currently available as a "grandfathered" drug product. There have been no recalls of the product due to safety or efficacy reasons.

The search strategies constructed for another nominated substance, sodium ascorbate, were used because magnesium chloride was nominated for use in combination with this substance via the same ROA. These database searches yielded 1426 references; 14 additional references were identified from ClinicalTrials.gov. After duplicates were removed, 1440 titles and abstracts were screened. After screening, the full text of 270 articles was reviewed. No studies were identified from the systematic literature review for sodium ascorbate that used magnesium chloride in combination with sodium ascorbate.

Characteristics of included studies

No studies were included from the literature review.

Use of magnesium chloride

No studies were included from the literature review.

Pharmacology and historical use

Six studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of magnesium chloride.

Per the 2014 Spanish Society of Medical Oncology (SEOM) guidelines, hypomagnesemia is defined as a plasma magnesium concentration below 1.7 mg/dL (or < 0.75 mmol/L or < 1.5 mEq/L); mild-moderate hypomagnesemia ranges between 1-1.6 mg/dL, with severe being anything < 1 mg/dL.[14] This deficiency has three pathophysiological mechanisms: decreased intake, diminished absorption, and increased excretion.[14] Symptoms do not typically manifest until the plasma concentration drops below 1.2 mg/dL, and hypomagnesemia is usually accompanied by other electrolyte disorders such as hypokalemia and hypocalcemia.[14] For the treatment of asymptomatic or non-severe hypomagnesemia, the authors recommended oral supplementation with magnesium chloride, magnesium lactate, or magnesium oxide.[14] However, when patients are symptomatic or the magnesium deficiency is severe, intravenous magnesium sulfate is the preparation of choice.[14]

In 2020, the American Society for Parenteral and Enteral Nutrition (ASPEN) released recommendations for refeeding syndrome.[15] The authors proposed that the diagnostic criteria for refeeding syndrome be a "decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by 10%-20% (mild), 20%-30% (moderate), or > 30% and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamine deficiency (severe), occurring within 5 days of reintroduction of calories."[15] Populations that were identified as at risk for refeeding syndrome include anorexia nervosa; mental health disorders; alcohol and substance-use disorder; bariatric surgery and bowel resections; malabsorption syndromes (such as celiac disease); starvation in protest, famine, and migration; child abuse and starvation; military recruits; athletes; patients with renal failure or on hemodialysis; critically ill patients; patients with malignancy; and patients in the emergency department.[15] In the 2017 guidelines for nutrition in cancer patients published by the

European Society for Clinical Nutrition and Metabolism (ESPEN), the authors discussed magnesium requirements in the prevention of refeeding syndrome in cancer patients.[16] Per these guidelines, they recommended magnesium as one of the electrolytes that "should be monitored and substituted, if necessary, by the oral, enteral, or parenteral route."[16] While they did not recommend a specific magnesium product, the requirement is approximately 0.2 mmol/kg/day if supplied via an intravenous route, or 0.4 mmol/kg/day if supplied via an oral route.[16]

In 2018, a set of guidelines on pediatric parenteral nutrition was published by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), ESPEN, the European Society of Paediatric Research (ESPR), and the Chinese Society of Parenteral and Nutrition (CSPEN).[17] The authors noted that the magnesium laboratory reference values in newborns are higher than adults, with a recent suggestion of a normal range of 0.7-1.5 mmol/L for premature and term newborns during their first 2 weeks of life.[17] They noted that the requirements are typically based on data from enteral nutrition and that magnesium retention ranges from 0.08 mmol/kg/day in infants who are fed human milk, compared to 0.15 mmol/kg/day in premature infants who are fed preterm infant formulas.[17] In situations where the mother has received magnesium sulfate therapy and the preterm newborn has been exposed to this (such as preeclampsia or tocolysis), the newborn may have high magnesium levels in their first days of life.[17] When you couple this with low postnatal glomerular filtration rates during their first week of life, these newborns have limited ability to excrete excessive magnesium, which must be taken into account when considering the magnesium intake.[17] The authors stated that while magnesium may be provided using magnesium sulfate or magnesium chloride salt forms, magnesium chloride may increase the risk of metabolic acidosis by increasing the anion gap.[17] As a result, magnesium is usually provided as magnesium sulfate, with few issues in compatibility.[17] Their suggested parenteral intake for magnesium varied based on age: 0.1-0.2 mmol/kg/day for preterm infants during the first days of life; 0.2-0.3 mmol/kg/day for growing premature infants; 0.1-0.2 mmol/kg/day for 0-6 months; 0.15 mmol/kg/day for 7-12 months; and 0.1 mmol/kg/day for 1-18 years .[17]

While intravenous magnesium appears to be commonly provided via the sulfate salt form, a case report was identified where magnesium chloride was suggested as an alternative in cases where the patient presents with an allergy to magnesium sulfate.[18] In this case report, the patient tolerated the magnesium chloride infusion well, with no evidence of allergy; the authors did note that allergy to magnesium sulfate is very rare, with "only 3 cases described in the literature."[18] In a couple of review articles, the authors stated that severe hypomagnesemia should be treated via the parenteral route with magnesium chloride because magnesium sulfate may aggravate hypocalcemia due to the binding of sulfate anions to calcium in the serum and urine.[7,19] In addition, magnesium sulfate is preferred for parenteral nutrition because it provides magnesium plus sulfate ions; however, when mixed with calcium chloride, the calcium and sulfate will precipitate quickly.[7]

Table 3. Types of studies

No studies included

Table 4. Number of studies by country

No studies included

Table 5. Summary of included studies

No studies included

Table 6. Dosage by indication – US

No studies included

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No studies included

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No studies included

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Sixteen SMEs discussed magnesium chloride. Amongst these 16 SMEs, there were 13 pharmacists and 3 naturopathic doctors. The SMEs specialized and/or were board-certified in naturopathy, nutrition, pediatrics, and sterile compounding, working in academia, academic medical centers, compounding pharmacies, consultancy, hospitals/health systems, pharmacy/pharma company, and private practice/clinic. The SMEs had been in practice for 7 to 44 years.

Magnesium chloride is a supplement used to treat and prevent hypomagnesemia. The SMEs commented that magnesium supplementation presents several challenges. Firstly, because magnesium is eliminated quickly from the body, it must be given slowly and continuously. Secondly, if provided orally, magnesium has a laxative effect; this creates a vicious cycle where the patient loses more magnesium and

can result in acidosis due to the loss of bicarbonate in the stool. However, the SMEs said that they do not worry about magnesium chloride itself causing metabolic acidosis. One medical condition that displays a drop in magnesium concentration is refeeding syndrome. Another SME said that they are now seeing more short-bowel patients, a lot of intestinal failure, and much higher magnesium needs.

Magnesium is also used as part of a "modified Myer's Cocktail," composed of calcium, magnesium, trace minerals, and vitamins B and C. One SME prescribed this combination for acute infection, or those recovering from an infection. They also prescribed magnesium for chronic fatigue and chronic hepatitis C; the latter was before hepatitis C had an effective treatment.

Some SMEs commented that the salt form used for magnesium did not really matter, that the idea is to get magnesium in whatever form is commercially available. However, other SMEs expressed concerns that practitioners may not consider changes in stability and compatibility when using magnesium chloride as opposed to the more familiar magnesium sulfate, or that facilities may not inform them that a change in salt form has been made. A SME said that while they happen to use a facility that is good at communication, home infusion companies may be less knowledgeable about switching between salt forms: "They tend to think the salt is the same thing and don't realize it might affect some other issues." Magnesium chloride has less data regarding stability and compatibility, and one SME said that this caused issues when they had to use magnesium chloride due to a shortage of magnesium sulfate. They did not recall any changes in doses between the two salt forms, though they did have to convert to milliequivalents whereas with magnesium sulfate they use milligrams.

For administration of magnesium as part of total parenteral nutrition, SMEs differed on the relevancy of salt form. One SME pointed out that chloride salts tend to be a challenge when trying to include lipids. If there is too much magnesium or if it is a divalent cation, it can disrupt the lipid and cause it to crack. Another SME commented that magnesium doses are typically small, so they would not be concerned with the acid-base balance stating that they would be more concerned about chloride provided with a maintenance IV fluid, especially for patients in the emergency room or intensive care unit receiving volume resuscitation. However, pediatric patients are more sensitive to different salt forms when compared to adults, and one SME who worked with neonates expressed concern about balancing the chloride to acetate ratio in this patient population. In addition, some patients only have one IV line (such as neonatal patients), therefore being able to put everything into one solution is more important.

Regarding the nominated combination product with magnesium chloride hexahydrate, Vitamin B complex, and Vitamin C as an injectable product, one SME said that they see no value in the combination and do not understand why someone would want this product: "I feel like you'd really be better off having more flexibility in your dosing of those agents than if it's in a fixed combination. Especially when you look at magnesium." Overall, they felt that it made more sense to do something more individualized.

Results of survey

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

The survey respondent used magnesium chloride as an intramuscular injection for muscle cramps, an indication that was not nominated.

The one survey respondent utilized compounded magnesium chloride due to lack of commercial products in an appropriate dosage form. Refer to Table 13 for reasons for using compounded magnesium chloride. An explanation for using compounded magnesium chloride due to lack of appropriate commercial products was not provided.

The respondent did not stock non-patient-specific compounded magnesium chloride at their practice.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Responses, n (N=1)**
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Naturopathic Doctor (ND)	1
Nurse Practitioner (NP)	0
Physician Assistant (PA)	0
Practice Setting	**Responses, n (N=1)**
Physician office or private practice	1
Outpatient clinic	0
Hospital or health system	0
Academic medical center	0
Emergency room	0
Operating room	0

Table 12. Conditions for which magnesium chloride prescribed or administered

Condition	Responses, n (N=1)
Electrolyte supplementation	0
Muscle cramps[a]	1
No Response	0

[a]Condition not nominated.

Table 13. Reasons for using compounded magnesium chloride

Reason	Responses, n (N=1)
Commercial product not available in desired dosage form, strength or combination	1
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	0
No commercial products	0

Table 14. Use of non-patient-specific compounded magnesium chloride

Do you stock non-patient-specific compounded magnesium chloride at your practice?	Responses, n (N=1)
Yes	0
No	1

CONCLUSION

Magnesium chloride was nominated for inclusion on the 503B Bulks List as intravenous and intramuscular injections for electrolyte supplementation and vitamin deficiency, respectively. Magnesium chloride is available in the US as an unapproved drug as a 200 mg/mL solution for intravenous injection. Magnesium chloride is available in the nominated dosage form and ROA in Belgium and Canada.

From the interviews, magnesium sulfate is the salt form used most commonly, with most SMEs either having never used magnesium chloride, or having only used it in situations where magnesium sulfate was not available. In general, when asked about magnesium chloride, SMEs expressed concern with the lack of familiarity with the salt form and an absence of compatibility data. They indicated that this could be a problem if people treated magnesium chloride the same as magnesium sulfate, instead of making necessary adjustments or informing practitioners of the switch. While most SMEs were not concerned about the presence of chloride in the admixture, stating that the dose of magnesium should be small enough not to throw off the acetate to chloride ratio, the SME who specialized in pediatrics and neonatal patients commented that their patients are more sensitive to chloride salts, and with fewer access points to administer medication, incompatibilities with salt forms is a bigger deal. While most of the conversations focused on the administration of magnesium chloride to replete magnesium levels, the SME asked about the use as an intramuscular injection with Vitamin B complex and Vitamin C responded that they thought it would be better to do something more individualized, rather than administering a fixed combination.

From the survey responses, the 1 respondent used magnesium chloride for muscle cramps, an indication that was not nominated. Lack of commercial products in an appropriate dosage form was the reason for using the compounded magnesium chloride product over an FDA-approved product.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
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.
6. Bashuk RG, Krendel DA. Myasthenia gravis presenting as weakness after magnesium administration. *Muscle & nerve.* 1990;13(8):708-712.
7. Chernow B, Smith J, Rainey TG, Finton C. Hypomagnesemia: implications for the critical care specialist. *Critical care medicine.* 1982;10(3):193-196.
8. Dubé L, Granry J-C. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* 2003;50(7):732-746.
9. Gums JG. Clinical significance of magnesium: a review. *Drug Intell Clin Pharm.* 1987;21(3):240-246.
10. Idama TO, Lindow SW. Magnesium sulphate: a review of clinical pharmacology applied to obstetrics. *Br J Obstet Gynaecol.* 1998;105(3):260-268.
11. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2004;28(6):S39-S70.
12. Osada H, Watanabe Y, Nishimura Y, Yukawa M, Seki K, Sekiya S. Profile of trace element concentrations in the feto-placental unit in relation to fetal growth. *Acta Obstet Gynecol Scand.* 2002;81(10):931-937.
13. Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington DC: National Academies Press (US); 1997.
14. De las Peñas R, Escobar Y, Henao F, Blasco A, Rodríguez CA. SEOM guidelines on hydroelectrolytic disorders. *Clinical and Translational Oncology.* 2014;16(12):1051-1059.
15. da Silva JSV, Seres DS, Sabino K, et al. ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutr Clin Pract.* 2020;35(2):178-195.
16. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr.* 2017;36(1):11-48.
17. Mihatsch W, Fewtrell M, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Calcium, phosphorus and magnesium. *Clin Nutr.* 2018;37(6):2360-2365.

18. Fragkos K, Mehta S, Di Caro S, Rahman F, Dziadzio M, Lukawska J. Magnesium sulphate allergy and subsequent tolerance to magnesium chloride in a patient with intestinal failure. *Clinical and Experimental Allergy.* 2017;47(12):1689-1690.

19. Seo JW, Park TJ. Magnesium metabolism. *Electrolyte and Blood Pressure.* 2008;6(2):86-95.

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 3, 2020
- Date last searched: March 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 354
- Note: The search strategy for another nominated substance, sodium ascorbate, was used because magnesium chloride was nominated for use in combination with this substance via the same ROA

1	ascorbic acid/	41724
2	as#orb$.tw.	40233
3	xyloascorb$.tw.	3
4	(vitamin$ adj2 c).tw.	20396
5	or/1-4	66350
6	exp administration, intravenous/	141842
7	infusions, parenteral/	26195
8	infusions, intravenous/	54478
9	injections/	42187
10	injections, intramuscular/	30789
11	injections, intravenous/	81384
12	inject$.tw.	654716
13	infusion$.tw.	226719
14	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11072
15	intravenous$.tw.	308002
16	intra venous$.tw.	479
17	intravascular$.tw.	43024
18	intra vascular$.tw.	254
19	intramuscular$.tw.	46814

20	intra muscular$.tw.	618
21	or/6-20	1177674
22	drug therapy/	30353
23	primary prevention/	18152
24	pre-exposure prophylaxis/	1937
25	immunomodulation/	6213
26	de.fs.	2948872
27	dt.fs.	2183728
28	ad.fs.	1393168
29	tu.fs.	2190900
30	pc.fs.	1263942
31	therap$.tw.	2355879
32	treat$.tw.	4670699
33	prevent$.tw.	1202938
34	prophyla$.tw.	144654
35	or/22-34	9778696
36	exp ascorbic acid deficiency/	3908
37	exp neoplasms/	3290888
38	exp inflammation/	330064
39	critical illness/	27797
40	common cold/	4184
41	influenza, human/	48109
42	exp antineoplastic protocols/	137787
43	chemotherapy, adjuvant/	39858
44	consolidation chemotherapy/	519
45	induction chemotherapy/	2565

46	maintenance chemotherapy/	1589
47	exp immune system/	1137127
48	((as#orb$ or vitamin c) adj3 (deficien$ or deplet$)).tw.	1874
49	avitaminosis.tw.	517
50	hypovitamin$.tw.	2125
51	hypoascorbemi$.tw.	6
52	scurv$.tw.	1413
53	scorbutus.tw.	24
54	cancer$.tw.	1472426
55	malignan$.tw.	490030
56	neoplas$.tw.	229979
57	tumo?r$.tw.	1457134
58	sepsis$.tw.	82046
59	septic?emi$.tw.	18738
60	bacter?emi$.tw.	28100
61	endotox?emi$.tw.	8476
62	(common adj3 cold).tw.	3131
63	chemotherap$.tw.	345153
64	flu.tw.	10741
65	influenza?.tw.	102079
66	or/36-65	5103172
67	and/5,21,35,66	755
68	exp animals/ not humans/	4674491
69	67 not 68	392
70	limit 69 to english language	354

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 944
- Note: The search strategy for another nominated substance, sodium ascorbate, was used because magnesium chloride was nominated for use in combination with this substance via the same ROA

1	ascorbic acid'/mj	36514
2	sodium ascorbic acid cotransporter'/de	213
3	ascorb*':ti,ab,tn	59489
4	askorb*':ti,ab,tn	51
5	xyloascorb*':ti,ab,tn	7
6	(vitamin* NEAR/2 c):ti,ab,tn	31787
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	92701
8	parenteral drug administration'/de	2103
9	intramuscular drug administration'/de	71554
10	intravascular drug administration'/exp	417233
11	injection'/exp	247471
12	inject*':ti,ab	1081672
13	infusion*':ti,ab	352385
14	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18102
15	intravenous*':ti,ab	482382
16	intra venous*':ti,ab	1433
17	intravascular*':ti,ab	67425
18	intra vascular*':ti,ab	675
19	intramuscular*':ti,ab	74319
20	intra muscular*':ti,ab	1269
21	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	2062203

22	drug therapy'/de	711290
23	pre-exposure prophylaxis'/de	3891
24	immunomodulation'/de	79019
25	drug dose':lnk	621716
26	drug administration':lnk	1717677
27	drug therapy':lnk	3841536
28	prevention':lnk	1159372
29	therap*':ti,ab	4072661
30	treat*':ti,ab	7765275
31	prevent*':ti,ab	1876511
32	prophyla*':ti,ab	257381
33	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	13040741
34	ascorbic acid deficiency'/exp	5948
35	neoplasm'/exp	5031993
36	inflammation'/exp	3688224
37	critical illness'/de	28545
38	common cold'/de	9670
39	influenza'/exp	96198
40	antineoplastic protocol'/de	204
41	cancer chemotherapy'/exp	440847
42	immune system'/exp	2236396
43	((ascorb* OR askorb* OR 'vitamin c') NEAR/3 (deficien* OR deplet*)):ti,ab	3257
44	avitaminosis':ti,ab	1366
45	hypovitamin*':ti,ab	4256
46	hypoascorbem*':ti,ab	12
47	hypoascorbaem*':ti,ab	0

48	scurv*':ti,ab	2518
49	scorbutus':ti,ab	36
50	cancer*':ti,ab	2494950
51	malignan*':ti,ab	836835
52	neoplas*':ti,ab	368059
53	tumor*':ti,ab	1967922
54	tumour*':ti,ab	425589
55	sepsis*':ti,ab	147991
56	septicemi*':ti,ab	18422
57	septicaemi*':ti,ab	9533
58	bacteremi*':ti,ab	33827
59	bacteraemi*':ti,ab	9022
60	endotoxemi*':ti,ab	10204
61	endotoxaemi*':ti,ab	1320
62	(common NEAR/3 cold):ti,ab	5036
63	chemotherap*':ti,ab	634337
64	flu':ti,ab	19747
65	influenza*':ti,ab	141141
66	#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 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65	10244586
67	#7 AND #21 AND #33 AND #66	1907
68	[animals]/lim NOT [humans]/lim	5999949
69	#67 NOT #68	1198
70	#67 NOT #68 AND [english]/lim	944

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded magnesium chloride. 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 magnesium chloride to your patients?

    - o Yes
    - o No

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

    - o Intramuscular injection
    - o Intravenous injection
    - o None of the above

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

    - o Electrolyte supplementation
    - o Other (please explain) _____

5. I use compounded magnesium chloride 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 magnesium chloride.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded magnesium chloride at your practice?

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

7. I obtain compounded magnesium chloride 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.