Summary Report

Copper gluconate

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
IV	Intravenous
IRB	Institutional Review Board
OTC	Over-the-counter
PN	Parenteral nutrition
ROA	Route of administration
RYGB	Roux-en-Y gastric bypass
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 copper gluconate; UNII code: RV823G6G67), 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 copper gluconate 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 copper gluconate 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 copper gluconate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Copper gluconate was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA).

Copper gluconate was nominated for nutritional supplementation and treatment of copper deficiency via a 0.4 mg/mL intravenous (IV) injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of copper gluconate.[6,7]

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

- The compounded product may be the only thing to effectively treat the indication
- A patient may need a prescribed dosage form or strength not available commercially
- Possible patient sensitivities or allergies to inactive ingredients
- Manufacturer backorders

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of copper gluconate 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 copper gluconate; name variations of copper gluconate 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 copper gluconate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: copper gluconate; IV administration or therapeutic use; and copper deficiency (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 December 11, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 7, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on November 7, 2019 for clinical practice guidelines that recommended the use of copper gluconate.

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 copper gluconate 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 copper gluconate 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 copper gluconate 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 copper gluconate; setting; total number of patients; number of patients who received copper gluconate; patient population; indication

for use of copper gluconate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of copper gluconate in a combination product; use and formulation of copper gluconate in a compounded product; use of copper gluconate 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 copper gluconate was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use copper gluconate: endocrinology, gastroenterology, naturopathy, nutrition, and bariatric surgery. 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 copper gluconate 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

- Copper gluconate is not available as an FDA-approved product in the nominated dosage form and ROA. However, cupric chloride is available as an IV injectable product (0.4 mg/mL) to be added to parenteral nutrition (PN) to prevent copper deficiency.
- Copper gluconate is not available as an OTC product in the US. However, it is available in some oral multi-vitamin products.
- There is a current United States Pharmacopeia (USP) monograph for copper gluconate.
- Copper gluconate is not available in any of the national medical registries searched. It is available as part of an electrolyte infusion with other active substances in Belgium, Hong Kong, and UK.

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 145 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 134 titles and abstracts were screened. After screening, the full text of 27 articles was reviewed. Finally, 1 study was included. Twenty-six studies were excluded for the following reasons: wrong dosage form or ROA (17 studies); language other than English (4); wrong study design (3); copper gluconate only mentioned briefly (1); wrong substance (1).

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

Characteristics of included studies

The 1 included descriptive study was published in the US in 2015.

One patient was described in the included study.

Outcome measure was resolution of cytopenias.

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

Use of copper gluconate

One patient received copper gluconate as a treatment for copper deficiency.

Refer to Table 6 for summaries of dosage by indication.

Copper gluconate was not used as a compounded product, nor was it used in a combination product.

In the 1 study, the authors' concluding statement recommended the use of copper gluconate for the treatment of copper deficiency.[8] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

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

In the general patient population, copper deficiency is not a common concern due to copper being abundant in food items such as legumes, potatoes, nuts, seeds, beef, and wheat.[9] However, morbidly obese patients are at higher risk due to micronutrient malabsorption.[10] In a 2016 review by Kumar, it was noted that "up to two-thirds of potential bariatric surgery candidates can be deficient in [copper]," with gastric bypass procedures such as Roux-en-Y gastric bypass (RYGB) further aggravating the problem after surgery.[9,10] Micronutrient deficiency is exacerbated by RYGB "through reduced intake, reduced absorption due to the exclusion of the duodenum and proximal jejunum which are the predominant sites for Cu [copper] absorption, or due to excess zinc intake which interferes with copper absorption."[9]

Asymptomatic copper deficiency is common in patients after receiving RYGB, while symptomatic copper deficiency is more rare, in addition to being difficult to diagnose; delays in diagnosis and treatment lead to patients suffering permanent neurological disabilities.[9] To complicate matters, a clinical diagnosis of copper deficiency cannot be made until other micronutrient deficiencies (such as iron, vitamin B12, and thiamine) have been ruled out or corrected.[9] As a result, the American Society for Metabolic and Bariatric Surgery (ASMBS), the British Obesity and Metabolic Surgery Society (BOMSS), and the Obesity Society have provided recommendations for all RYGB and biliopancreatic diversion/duodenal switch (BPD/DS) patients to receive at least 2 mg of copper daily, 200% of the recommended daily allowance.[9-12] Per the 2020 ASMBS guidelines, "copper gluconate or sulfate is the recommended source of copper for supplementation."[11] Because zinc supplementation can interfere with copper absorption, it is recommended to supplement 1 mg of copper for every 8-15 mg of elemental zinc.[11,12]

When it comes to monitoring, BOMSS has different recommendations from the ASMBS. The ASMBS does not recommend routine monitoring of copper levels post-bariatric surgery unless the patient presents with unexplained anemia, neutropenia, myeloneuropathy, or impaired wound healing.[9] In contrast, BOMSS recommends annual monitoring of serum copper in patients who have had RYGB procedures.[9,12]

To replete copper in patients diagnosed with copper deficiency, the 2020 ASMBS guidelines provide different regimens depending on the degree of deficiency. Mild-to-moderate copper deficiency can be supplemented with oral copper gluconate or sulfate (3-8 mg/day) until patient indices return to normal.[11] In patients with severe deficiency, intravenous copper (2-4 mg/day) should be administered for 6 days or until the serum levels return to normal and neurological symptoms have resolved.[11] Regardless of severity, copper levels should be monitored every 3 months after they return to normal.[11]

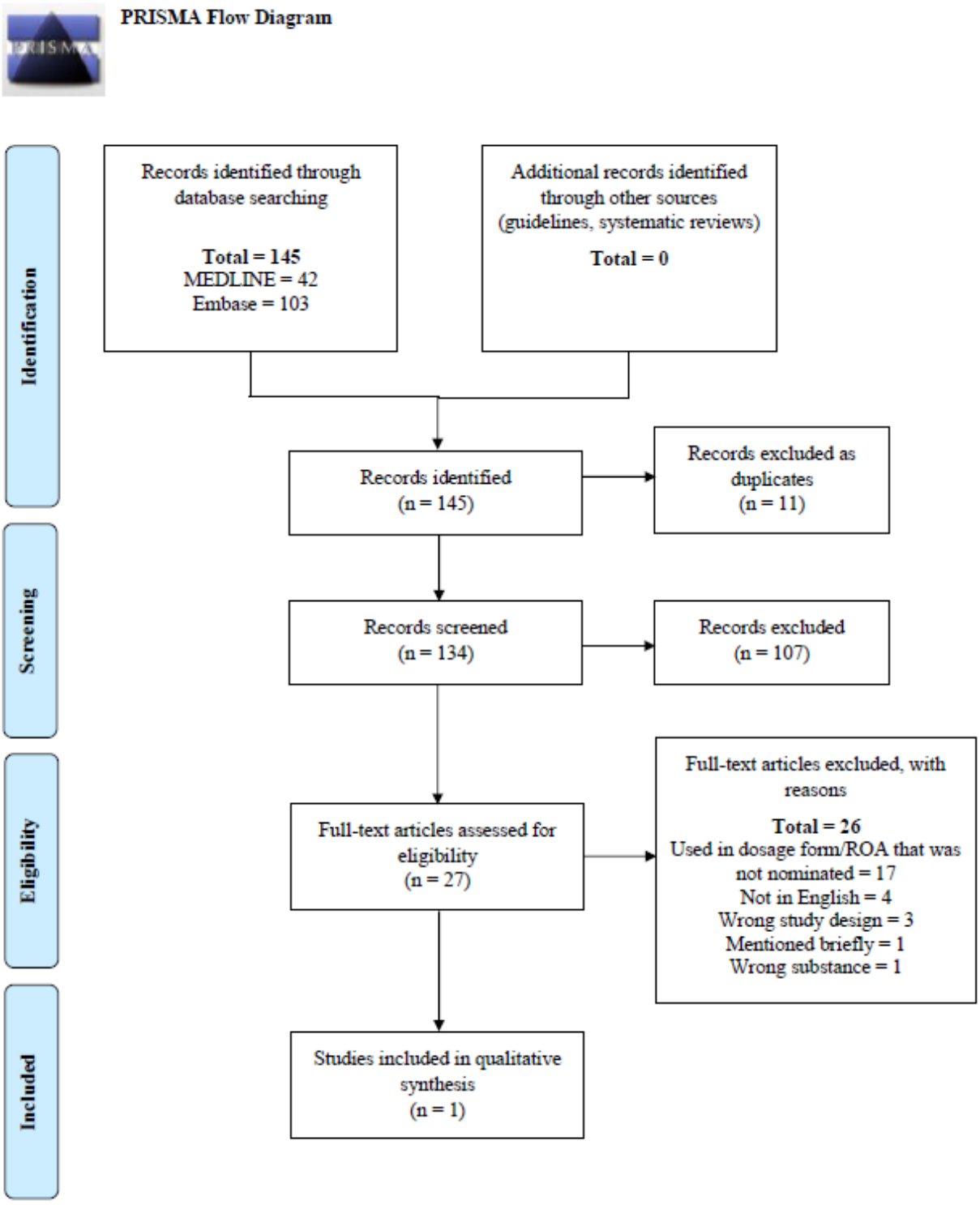
While bariatric procedures are more common causes of copper deficiency, it has also been occasionally reported in children on long term PN.[13] In 2018, a set of guidelines on pediatric parenteral nutrition was produced by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), the European Society for Clinical Nutrition and Metabolism

(ESPEN), the European Society of Paediatric Research (ESPR), and the Chinese Society of Parenteral and Nutrition (CSPEN).[13] In this guideline, daily parenteral copper requirements were 40 mcg/kg for preterm infants and 20 mcg/kg for term infants and children, with a maximum daily dose of 0.5 mg for daily supplementation.[13]

In the ESPEN guidelines on PN in intensive care patients, it was noted that "the FDA-approved trace element formulation results in relatively high levels of copper and manganese, which may be associated with toxicity during prolonged home [parenteral nutrition]."[14] However, while there are several trace element combination products that are available for parenteral administration, they are not FDA-approved. In the ESPEN guidelines concerning chronic intestinal failure in adults, the authors point out that copper supplementation may have to be decreased in patients with cholestatic liver disease, but increased in cases of prolonged gastrointestinal fluid losses.[15] They noted that patients are at increased risk for copper toxicity with long-term PN because PN-associated liver dysfunction and cholestasis causes hepatic copper accumulation; therefore, copper in a typical adult parenteral nutrition formulation should be limited to less than 0.1 mg/day.[15]

In a position paper from the American Society for Parenteral and Enteral Nutrition (ASPEN) on trace element recommendations, the concentration of copper in the multi-trace and individual element products available in North America ranged from 0.2-2 mg/mL.[16] The salt form of the multi-trace products was not specified; individual copper products were cupric chloride or cupric sulfate.[16]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[8]	1
Observational	0
Experimental	0

Table 4. Number of studies by country

Country	**Number of Studies**
US[8]	1
	Total US: 1 Total Non-US Countries: 0

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Copper deficiency					
Sonu *et al.*, 2015, US[8]	–	1 In-patient post-gastric bypass presenting with pancytopenia (0%, 66 y)	• Copper gluconate (1)	Resolution of cytopenias	Copper deficiency may mimic myelodysplastic syndrome and should always be ruled out

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

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Copper deficiency[8]	–	–	–	–	–

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No 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. Eighteen SMEs discussed copper gluconate. Amongst these 18 SMEs, there were 2 medical doctors, 14 pharmacists, 1 physician assistant, and 1 doctor of philosophy. The SMEs specialized and/or were board-certified in critical care, gastroenterology, hepatology, nutrition, occupational medicine, pediatrics, primary care/family medicine, psychiatry, and sterile compounding, working in academia, academic medical centers, compounding pharmacies, consulting, hospitals/health system, pharmacy/pharma company, and private practice/clinic. The SMEs had been in practice for 7 to 44 years.

According to the SMEs, there are two reasons to use IV copper: for maintenance to prevent deficiencies and to treat clinical deficiencies. An example of the first would be patients on long-term home PN, some of whom are on PN for life. One SME noted that the current trace element formulation contains a little too much manganese, zinc, and copper. Therefore, to prevent chronic toxicity, practitioners may choose to dose the trace elements individually, which can open the door for needing IV copper and treating deficiencies. Another benefit of dosing trace elements individually is that some regimens use higher doses in the beginning, and taper the dose down, something that is challenging to do in total parenteral nutrition (TPN). An example of the second would be patients with bariatric surgery and short bowel issues who cannot absorb copper and need alternative replacement, especially if the patient is non-compliant with their vitamin regimens or has a co-disease, such as fibrosis or liver disease. One specific bariatric surgery, RYGB, was specified as having a higher risk, but deficiency can occur with many of the bariatric surgeries. SMEs reported that they also use oral copper supplementation in these patients, though it is not something typically stocked by many community pharmacies. Another cause of copper deficiency is when patients have been taking a large about of zinc prophylactically for viruses or are told to do so for wound healing. Burn units also use a lot of copper, and they prefer to use the IV product via the oral route.

Severe copper deficiency can result in neuropathies. As a result, practitioners prefer to use the IV form for faster resolution of the symptoms before switching to oral for maintenance. Additionally, the SMEs said that for patients with a severe deficiency, the multi-trace product is probably not adequate for repletion; “at least in adults, we haven’t had to add extra cupric chloride. In pediatrics…the commercially available trace element ‘cocktails’ don’t meet the needs of the patients.” Other potential consequences of copper deficiency include hematologic issues such as anemia or neutropenia, optic neuropathy, bone-related issues, and uropathy; as a result, not only does the deficiency need to be treated, but the patient needs to have a vitamin or multi-vitamin for when they transition off PN.

When using IV copper repletion, even for patients with a severe deficit, practitioners typically administer 1-2 mg IV once daily for about a week; there is no hurry or benefit to using either a higher or more frequent dosing, since the body does not assimilate it. After a week, the supplement is typically switched to oral or enteral (20-40 mcg/kg/day) and continued for about 4 weeks before they re-check the levels.

This dose may be reduced in patients who have some sort of liver dysfunction, though when the patients recover, they may have a higher requirement. Copper is eliminated through the body's biliary system; as a result, if the patient has bad cholestasis or other liver problems, it may be withheld completely because the body is unable to effectively eliminate copper in these conditions. If possible, they prefer to avoid using IV if possible, "it is one less break in the line if they still have a central catheter. We don't have that many kids who get copper who aren't on PN." In pediatric patients, if they are not on parenteral nutrition, but cannot meet their vitamin needs through multi-vitamins, they may receive the IV product enterally.

In hospital and outpatient infusion centers, they use whatever IV copper products that they have; the salt form is irrelevant since they dose based on elemental copper. Typically, the IV copper that is accessible is manufactured cupric chloride, but this changes all of the time based on what is available and what is on backorder, for both single-entity trace elements and multi-trace products. Single-entity trace elements have also been reformulated and gone up in price. The manufacturer of the commercially available multi-trace element product, American Regent, is supposed to be coming out with a new adult formulation that will be more consistent with current recommendations and will hopefully be helpful with patients on long-term PN and potentially decrease the need for individual trace element products. In several SMEs' opinions, they suspect that American Regent will come out with a pediatric or neonatal product that is more consistent with recommendations in the future as well.

One SME said that 68% of patients with attention deficit hyperactivity disorder (ADHD) have elevated copper levels which can cause hyperactivity and high levels of norepinephrine and adrenaline. High levels of copper are also associated with panic and anxiety disorders; treatment focuses on use of zinc and vitamin B6. However, a bigger issue with copper is if the patient has Wilson's disease, a fatal disease where copper accumulates in the liver. Because of this accumulation, practitioners should rule out Wilson's disease before supplementing patients with low copper levels.

One issue SMEs discussed with compounded products, especially for large-volume parenteral, was stability, compatibility, and precipitation amongst salt forms. SMEs considered this a safety issue since a lot of the stability information for copper comes from copper sulfate but the FDA-approved copper is copper chloride and if they are using copper gluconate there are a lot of unknowns that need to be pursued. Additionally, individual trace elements are very concentrated, and it is challenging to measure the tiny amount of commercially available copper chloride to put into the bag. The amount of elemental copper that is available may be different, depending on the salt form; it would not be a one-to-one switch to use a different salt form.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which copper gluconate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded copper gluconate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded copper gluconate

No respondents to survey distributed via professional medical associations

CONCLUSION

Copper gluconate was nominated for inclusion on the 503B Bulks List for nutritional supplementation and treatment of copper deficiency via an IV injection. Copper gluconate is not approved in any of the national medical registries searched in the nominated dosage form and ROA.

From the literature review and interviews, copper deficiency is less problematic in the general population, but is more of a concern in patients who have undergone bariatric surgery (such as RYGB) or are reliant on long-term PN. Another factor that may contribute to copper deficiency is excess zinc intake, which may interfere with the absorption of copper. Copper deficiency is a diagnosis of exclusion, and a clinical diagnosis cannot be made until other micronutrient deficiencies have been ruled out or corrected. Multiple guidelines exist providing recommendations for bariatric surgery patients to orally supplement their copper intake after their procedures, though monitoring is not considered necessary unless the patient presents with symptoms. Typically, unless the patient is receiving PN already, the general consensus is that practitioners prefer to use oral copper for maintenance, and reserve IV copper for severe deficiencies that manifest in neuropathy, hematologic changes, bone-related issues, and uropathy. Typically, the product used for copper supplementation is either a multi-trace product or copper chloride, which is the FDA-approved copper product. SMEs expressed concerns about differences in salt forms regarding stability, compatibility, and precipitation, which would make them hesitant to substitute in copper gluconate unless necessary.

Zero people responded to the survey distributed via professional medical associations and available on the project website.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to December 10, 2019
- Date last searched: December 11, 2019
- Limits: Humans (search hedge); English language
- Number of results: 42

1	gluconates/	3522
2	(copper adj3 glucon$).tw.	43
3	or/1-2	3540
4	drug administration routes/	5600
5	exp administration, intravenous/	141216
6	infusions, parenteral/	26198
7	administration & dosage.fs.	1380854
8	infusion$.tw.	240527
9	inject$.tw.	721147
10	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11912
11	intravenous$.tw.	332325
12	intra venous$.tw.	564
13	intravascular$.tw.	46514
14	intra vascular$.tw.	296
15	drug therapy/	30252
16	nutrition therapy/	2192
17	nutritional support/	6068
18	exp parenteral nutrition/	23669
19	drug therapy.fs.	2161454
20	(nutrition$ adj2 (parenteral$ or supplement$ or support$)).tw.	36537

21	therap$.tw.	2658008
22	treat$.tw.	5272382
23	or/4-22	8358813
24	copper/	67164
25	(copper adj3 deficien$).tw.	2566
26	exp nutrition disorders/	343179
27	exp "feeding and eating disorders"/	29690
28	exp emaciation/	5735
29	hypocupremi$.tw	107
30	malnutrition$.tw.	37666
31	malnourish$.tw.	10341
32	anorexi$.tw.	32011
33	bulimi$.tw.	8179
34	emaciat$.tw.	1994
35	cachexi$.tw.	7447
36	((diet$ or eat$ or nutrition$) adj2 (deficien$ or disorder$ or insufficien$)).tw.	39271
37	or/24-36	498480
38	and/3,23,36	78
39	exp animals/ not humans/	4648880
40	38 not 39	53
41	limit 40 to english language	42

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: December 11, 2019
- Limits: Humans (search hedge); English language
- Number of results: 103
- Notes: Did not include third concept (indications) because specific Emtree term for 'copper gluconate', unlike in MEDLINE.

1	gluconate copper'/de	155
2	(copper NEAR/3 glucon*):ti,ab,tn	72
3	#1 OR #2	172
4	drug administration route'/de	7716
5	parenteral drug administration'/de	2056
6	intravascular drug administration'/de	306
7	intravenous drug administration'/de	391032
8	drug administration':lnk	1699419
9	inject*':ti,ab	1070335
10	infusion*':ti,ab	348851
11	(parenteral* NEAR/2 (administ* OR deliver*)):ti,ab	11179
12	intravenous*':ti,ab	476466
13	intra venous*':ti,ab	1418
14	intravascular*':ti,ab	66206
15	intra vascular*':ti,ab	670
16	drug therapy'/de	692877
17	drug therapy':lnk	3801187
18	nutrition supplement'/exp	17255
19	parenteral nutrition'/exp	49409
20	mineral supplementation'/de	1573
21	nutritional support'/de	18473

22	(nutrition* NEAR/2 (parenteral* OR supplement* OR support*)):ti,ab	52136
23	therap*':ti,ab	4005634
24	treat*':ti,ab	7646839
25	#4 OR #5 OR #6 OR #7 OR #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 OR #21 OR #22 OR #23 OR #24	12386788
26	#3 AND #25	134
27	[animals]/lim NOT [humans]/lim	5959680
28	#26 NOT #27	103

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded copper gluconate. 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 copper gluconate to your patients?

   - o Yes
   - o No

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

   - o Intravenous injection
   - o None of the above

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

   - o Copper deficiency
   - o Nutritional supplementation
   - o Other (please explain) _____

5. I use compounded copper gluconate 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 copper gluconate.
   - o Other (please explain) _____

6. Do you stock non-patient-specific compounded copper gluconate at your practice?

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

7. I obtain compounded copper gluconate 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.