Summary Report

Glucosamine sulfate potassium chloride and glucosamine sulfate sodium chloride

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
GSPC	Glucosamine sulfate potassium chloride
GSSC	Glucosamine sulfate sodium chloride
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of glucosamine sulfate potassium chloride (GSPC; UNII code: 15VQ11I66N) and glucosamine sulfate sodium chloride (GSSC; UNII code: 7RI65CXJ9S), which were 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 GSPC and GSSC are 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 GSPC and GSSC have 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 GSPC and GSSC and thereby assist the FDA to determine whether there is a need for the inclusion of these substances on the 503B Bulks List.

REVIEW OF NOMINATIONS

GSPC and GSSC were evaluated together in this report because most practitioners and studies do not provide information on or differentiate between the potassium and sodium chloride salt forms for glucosamine sulfate.

GSPC was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) and Olympia Compounding Pharmacy.

GSPC was nominated for the treatment of osteoarthritis and degenerative joint disease via a 200 mg/mL intramuscular and intravenous injection.

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

- There are no FDA-approved products that contain GSPC
- Compounded product may be the only product to effectively treat the indication for which it is intended
- Patient need for dosage form or strength, including a greater concentration, that is not available commercially
- Patient sensitivities to dyes, fillers, preservatives or other excipients in manufactured products
- Manufacturer backorder

GSSC was nominated for inclusion on the 503B Bulks list by the OFA.

GSSC was nominated for the treatment of osteoarthritis and degenerative joint disease via a 200 mg/mL intramuscular and intravenous injection.

Reasons provided for nomination to 503B Bulks List include:

- There are no FDA-approved products that contain GSSC
- 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

Nominators provided references from published literature to describe the pharmacology and support the clinical use of GSPC and GSSC.[6-9]

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of GSPC and GSSC 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 GSPC and GSSC; name variations of GSPC and GSSC 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 GSPC/GSSC. 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 four concepts: glucosamine; intravenous or intramuscular administration; therapeutic use; and osteoarthritis and degenerative joint disease (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 12, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 9, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on November 9, 2019 for clinical practice guidelines that recommended the use of glucosamine and provided sufficient dosing and administration instructions.

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 GSPC or GSSC were 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 GSPC or GSSC were 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 GSPC or GSSC were 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 GSPC or GSSC; setting; total number of patients; number of patients who received GSPC or GSSC; patient population; indication for use of GSPC or GSSC; dosage form and strength; dose; ROA; frequency and duration of therapy; use of GSPC or GSSC in a combination product; use and formulation of GSPC or GSSC in a compounded product; use of GSPC or GSSC 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 GSPC and GSSC were 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 GSPC and GSSC: naturopathy, orthopedics, primary care and internal medicine, and rheumatology. 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 GSPC and GSSC 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

- Neither GSPC nor GSSC are available as an FDA-approved product in the nominated dosage form and ROA.
- GSPC and GSSC are available as oral OTC products in the US.
- There is a current United States Pharmacopeia (USP) monograph for GSPC and GSSC.
- Neither GSPC nor GSSC are available in the nominated dosage form and ROA in any of the national medical registries searched. Glucosamine sulfate is available as an oral prescription product in Abu Dhabi, Ireland, Hong Kong, and Latvia.

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 247 references; 5 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 196 titles and abstracts were screened. After screening, the full text of 46 articles was reviewed. Finally, 2 studies were included. Forty-four studies were excluded for the following reasons: wrong study design (19 studies); wrong dosage form or ROA (11); GSPC or GSSC only mentioned briefly (8); duplicate study (1); GSPC or GSSC not used clinically (1); language other than English (1); GSPC or GSSC used as brand or proprietary product (1); wrong substance (1); incorrect salt form, or salt form not specified (1).

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

Characteristics of included studies

The 2 included studies were published in 1980 and 1994. There were 2 experimental studies, 0 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 2 studies were conducted in the following countries: Germany and Italy.

A total of 185 patients participated in the 2 included studies. The number of patients in each study ranged from 30 to 155.

Outcome measures differed among the included studies and included: degree of pain at rest, during movement, and the Algo-functional index of Lequesne.

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

Use of GSPC and GSSC

Fifteen patients received glucosamine sulfate as an experimental treatment for chronic osteoarthrosis, administered intramuscularly in 400 mg doses. Duration of treatment was 1 week. Seventy-three patients received glucosamine sulfate as an experimental treatment for gonarthrosis (osteoarthritis of the knee), administered intramuscularly in 400 mg doses. Duration of treatment was 6 weeks.

Refer to Table 7 for summary of dosage by indication.

GSPC and GSSC were not used as a compounded product, nor were they nominated as a combination product.

In 2 studies, the authors' concluding statement recommended the use of glucosamine sulfate for the treatment of chronic osteoarthrosis and knee osteoarthritis.[8,10] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 2 included studies, 3 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of glucosamine sulfate.

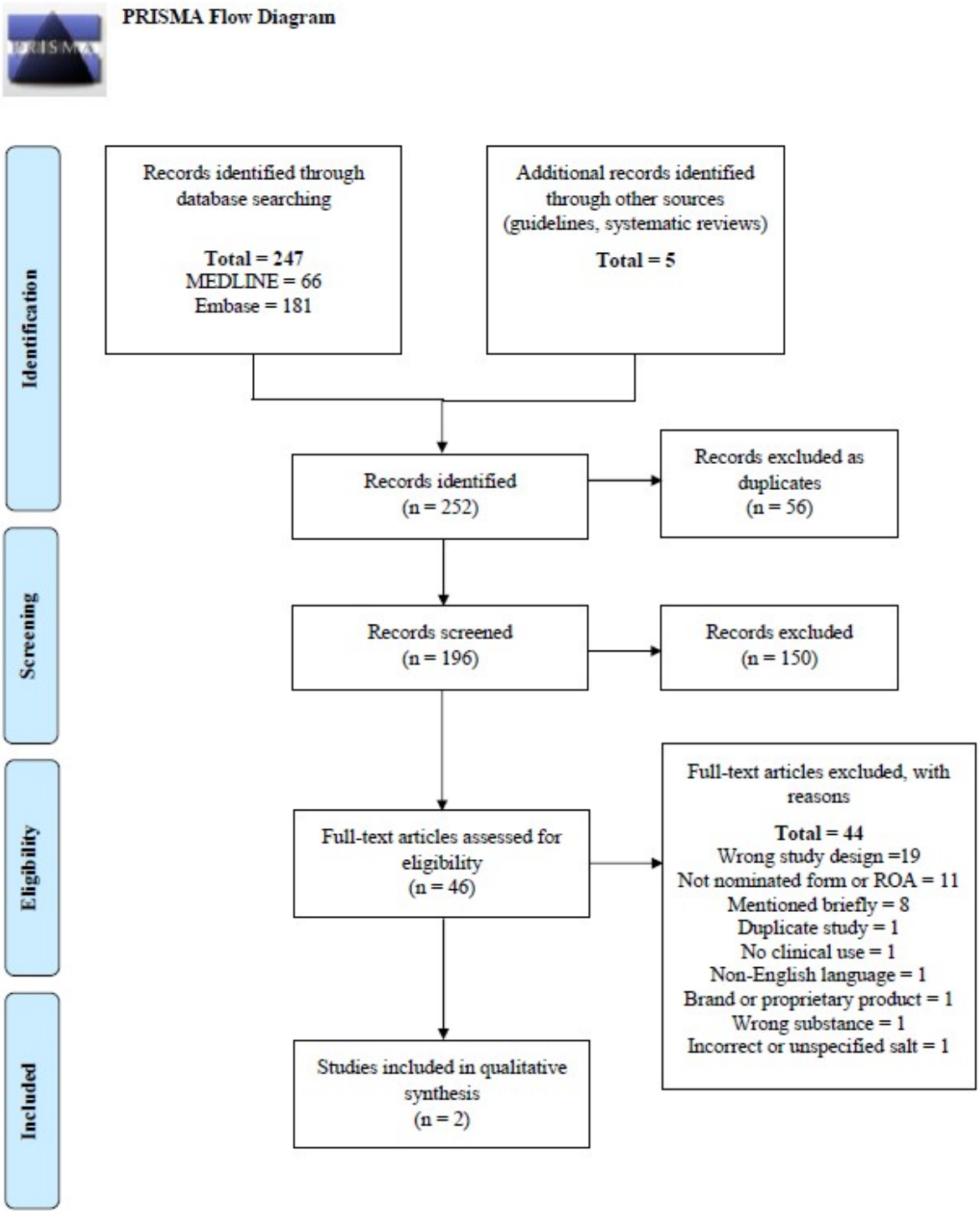
In 1994, McCarty noted that the first report of therapeutic use of glucosamine in humans was in 1969 by German researchers.[11] In this study, injectable glucosamine sulfate (400 mg) was given once daily via intra-articular, intravenous, or intramuscular routes in osteoarthritis patients; researchers reported improvements in pain and motility.[11] Since the 1969 German study was uncontrolled, it was difficult

to determine conclusions about the effectiveness of glucosamine in osteoarthritis.[11] Since this time, a wide variety of studies have been conducted with glucosamine, more commonly with the oral preparation.

In 2009, Altman commented in a review that sulfated glucosamine is very hygroscopic, therefore the pharmaceutical-grade glucosamine sulfate product is stabilized with sodium chloride in a product referred to as crystalline glucosamine sulfate (Rottapharm-Madaus, Monza, Italy).[12] Altman added that crystalline glucosamine sulfate has been shown to be effective in controlling osteoarthritis symptoms in the knee through randomized and controlled clinical trials and "is available as a prescription drug in Europe and elsewhere."[12] Furthermore, Altman discussed glucosamine sulfate that is stabilized by potassium chloride instead of sodium chloride and said "these products are available as supplements, but have either not been tested in pharmacokinetic studies or not been effective in clinical trials."[12] Another available salt form of glucosamine is glucosamine hydrochloride; Altman commented that this salt form is more readily available, easier to manufacture, and is often supplied in supplements as a combination with chondroitin sulfate; however, it "has not proven effective in several [osteoarthritis] trials."[12] It should be noted that the two trials mentioned by Altman, the Glucosamine Unum In Die Efficacy (GUIDE) and the National Institutes of Health-sponsored Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), which compared glucosamine sulfate to glucosamine hydrochloride with or without the addition of chondroitin sulfate, used oral glucosamine products, not injectable.

Due to discrepancies in glucosamine efficacy in studies sponsored by the industry compared to those publicly funded, the American College of Rheumatology expressed concerns about publication bias in their 2019 osteoarthritis guidelines.[13] As a result, glucosamine is strongly recommended against as a treatment for knee, hip, and hand osteoarthritis, though the authors noted that it is one of the most commonly used dietary supplements in the US and patients perceive it as effective.[13] The authors appeared to be focusing on oral glucosamine when making this recommendation; there was no mention of an injectable product.

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	0
Observational	0
Experimental[8,10]	2

Table 4. Number of studies by country

Country	**Number of Studies**
Germany[8]	1
Italy[10]	1
	Total US: 0 Total Non-US Countries: 2

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 1: Chronic osteoarthrosis					
Crolle and D'Este, 1980, Italy[10]	Controlled clinical trial	30 In-patients with chronic osteoarthritis (27%, range 49-88 y)	• Intramuscular glucosamine sulfate followed by oral glucosamine sulfate (12) • Intra-articular glucosamine sulfate followed by oral glucosamine sulfate (3) • Intramuscular piperazine/chlorbutanol (15)	Degree of pain at rest and during movement	Pure glucosamine sulfate, parenteral and oral, effectively managed the symptoms of osteoarthritis and improved articular function
Indication 2: Knee osteoarthritis					
Reichelt *et al.*, 1994, Germany[8]	Randomized, placebo-controlled double-blind	155 Out-patients with knee osteoarthritis (35%, range 19-75 y)	• Glucosamine sulfate (79) • Placebo: 0.9% saline (76)	Algo-functional index of Lequesne	Intramuscular glucosamine sulfate significantly improved symptoms of knee osteoarthritis

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

Table 6. Dosage by indication – US

No studies included

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Chronic osteoarthrosis[10]	400 mg/day	–	–	Intramuscular	7 days
Osteoarthritis of the knee[8]	800 mg/week	400 mg/2 mL	Solution	Intramuscular	6 weeks

Abbreviations: "–", not mentioned

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No compounded products from reported studies

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. Nine SMEs discussed GSPC and GSSC. Amongst the 9 SMEs, there were 5 medical doctors, 2 physician assistants, and 2 naturopathic doctors. The SMEs specialized and/or were board-certified in internal medicine, naturopathy, orthopedics, pain management, primary care/family practice, and rheumatology, working in academic medical centers, hospitals/health systems, and private practice/clinics. The SMEs had been in practice for 8 to 39 years.

All the SMEs were aware of the use of glucosamine sulfate in patients with arthritis, but none of them reported currently administering it as an injectable product. Two of the SMES stated that they had administered glucosamine sulfate as an intraarticular sterile injection for patients with osteoarthritis and degenerative joint disease, but not intramuscular or intravenous administration. The idea behind the intraarticular injection was that the patient would achieve a faster resolution or benefit when compared to receiving oral glucosamine alone. Frequency of administration was dependent upon patient response, with doses ranging between 3 times per week and 3 times bimonthly. The patient would also typically be receiving oral glucosamine in addition to the intraarticular injection, and after around 12 weeks the injections would be stopped while the patient continued with oral glucosamine alone. While these intraarticular injections have fallen out of favor with the introduction of commercial hyaluronic acid products, injectable glucosamine sulfate is still being used in addition to other injectable commercial products.

Other SMEs reported the lack of strong evidence supporting the use of glucosamine, with some studies showing effectiveness in only a third of patients who received it. In addition, these studies have predominantly focused on knee arthritis. However, some SMEs still use oral glucosamine sulfate in patients with arthritis. One SME said that if patients do not see a benefit within 3 months, then they likely will not see a response with further treatment. Despite the SMEs being skeptical about the efficacy of glucosamine, they noted that the patients like it, were typically fine spending money on it, and find it relatively harmless for the patients to take. However, there were SMEs who did not recommend glucosamine sulfate use at all, citing the lack of proven effectiveness. One SME said that the potential exception would be in the case of very pure glucosamine in combination with chondroitin, but overall, the studies have not been successful.

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 GSPC/GSSC prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded GSPC/GSSC

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded GSPC/GSSC

No respondents to survey distributed via professional medical associations

CONCLUSION

GSPC and GSSC were nominated for inclusion on the 503B Bulks List via an intramuscular and intravenous injection to treat osteoarthritis and degenerative joint disease. Neither GSPC nor GSSC are approved in any of the national medical registries searched.

From the literature review and interviews, glucosamine sulfate is administered via intraarticular, intravenous, intramuscular, and oral routes in osteoarthritis patients. Minimal information was available regarding the difference in the nominated salt forms (potassium chloride and sodium chloride), except that they are different stabilizing agents due to the hygroscopicity of glucosamine sulfate. Furthermore, an additional, non-nominated salt form (hydrochloride) was described as more readily available, easier to manufacture, and often part of supplements in combination with chondroitin sulfate, though it has not proven effective in multiple osteoarthritis trials. Most studies have been done with oral products, and due to disparity in study results, the 2019 American College of Rheumatology osteoarthritis guidelines expressed concern about publication bias and strongly recommended against glucosamine as treatment for knee, hip, and hand osteoarthritis. This recommendation was despite glucosamine being one of the most used dietary supplements in the US and patients viewing the product as effective. Amongst SMEs, opinions on the use of glucosamine sulfate varied as well. None of them reported currently using injectable glucosamine sulfate, but there were reports of past use of intraarticular glucosamine sulfate. While these injections were intended to add a clinical benefit in addition to hyaluronic acid or other commercial products, intraarticular glucosamine sulfate injections seemed to have fallen out of favor with the arrival of commercial hyaluronic acid products.

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

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. D'Ambrosio E, Casa B, Bompani R, Scali G, Scali M. Glucosamine sulphate: a controlled clinical investigation in arthrosis. *Pharmatherapeutica.* 1981;2(8):504-508.
7. Pournadeali K. Glucosamine sulfate: a review of efficacy for the pharmacy professional. *Int J Pharm Compd.* 1999;3(6):428-433.
8. Reichelt A, Forster KK, Fischer M, Rovati LC, Setnikar I. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. A randomised, placebo-controlled, double-blind study. *Arzneimittel-Forschung.* 1994;44(1):75-80.
9. Vajaradul Y. Double-blind clinical evaluation of intra-articular glucosamine in outpatients with gonarthrosis. *Clinical Therapeutics.* 1981;3(5):336-343.
10. Crolle G, D'Este E. Glucosamine sulphate for the management of arthrosis: A controlled clinical investigation. *Current Medical Research and Opinion.* 1980;7(2):104-109.
11. McCarty MF. The neglect of glucosamine as a treatment for osteoarthritis - a personal perspective. *Medical Hypotheses.* 1994;42(5):323-327.
12. Altman RD. Glucosamine therapy for knee osteoarthritis: pharmacokinetic considerations. *Expert Rev Clin Pharmacol.* 2009;2(4):359-371.
13. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res.* 2020;72(2):149-162.

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 12, 2019
- Limits: Humans (search hedge); English language
- Number of results: 66

1	exp glucosamine/	14362
2	glucosamin$.tw.	19857
3	or/1-2	28522
4	drug administration routes/	5604
5	exp administration, intravenous/	141262
6	infusions, parenteral/	26200
7	injections/	41949
8	injections, intramuscular/	30656
9	inject$.tw.	721471
10	infusion$.tw.	240596
11	perfusion.tw.	155963
12	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11915
13	intravenous$.tw.	332478
14	intra venous$.tw.	564
15	intravascular$.tw.	46533
16	intra vascular$.tw.	296
17	intramuscular$.tw.	51080
18	intra muscular$.tw.	702
19	or/4-18	1410674
20	drug therapy/	30270

21	drug effects.fs.	2928070
22	drug therapy.fs.	2162993
23	tu.fs.	2174725
24	administration & dosage.fs.	1381693
25	therap$.tw.	2660216
26	treat$.tw.	5276412
27	or/20-26	9522891
28	exp osteoarthritis/	60889
29	spondylosis/	2093
30	osteoarthrit$.tw.	62537
31	osteo arthrit$.tw.	412
32	osteoarthros$.tw.	3203
33	osteo arthros$.tw.	61
34	(degenerative adj2 (arthrit$ or arthros$ or joint?)).tw.	4883
35	((ankle or hand or hip or knee or shoulder or spine or spinal or temporomandibl$) adj2 (arthrit$ or arthros$)).tw.	9883
36	spondylosis.tw.	3137
37	or/28-36	100991
38	and/3,19,27,37	104
39	exp animals/ not humans/	4651026
40	38 not 39	79
41	limit 40 to english language	66

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: December 12, 2019
- Limits: Humans (search hedge): English language
- Number of results: 181

1	glucosamine'/exp	20632
2	glucosamin*':ti,ab,tn	24106
3	#1 OR #2	35584
4	drug administration route'/de	7716
5	parenteral drug administration'/de	2057
6	intramuscular drug administration'/de	71464
7	intravascular drug administration'/de	306
8	intravenous drug administration'/de	391063
9	inject*':ti,ab	1070663
10	infusion*':ti,ab	348932
11	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	17925
12	intravenous*':ti,ab	476601
13	intra venous*':ti,ab	1418
14	intravascular*':ti,ab	66240
15	intra vascular*':ti,ab	670
16	intramuscular*':ti,ab	72794
17	intra muscular*':ti,ab	1254
18	#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	2016977
19	drug therapy'/de	693349
20	add on therapy'/de	18329
21	drug comparison':lnk	592411
22	drug dose':lnk	619974

23	drug therapy':lnk	3802421
24	therap*':ti,ab	4007735
25	treat*':ti,ab	7650715
26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	11461764
27	osteoarthritis'/exp	132728
28	osteoarthrit*':ti,ab	92354
29	osteo arthrit*':ti,ab	924
30	osteoarthros*':ti,ab	4441
31	osteo arthros*':ti,ab	132
32	(degenerative NEAR/2 (arthrit* OR arthros* OR joint$)):ti,ab	7014
33	((ankle OR hand OR hip OR knee OR shoulder OR spine OR spinal OR temporomandibl*) NEAR/2 (arthrit* OR arthros*)):ti,ab	13800
34	spondylosis':ti,ab	4955
35	#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	164048
36	#3 AND #18 AND #26 AND #35	262
37	[animals]/lim NOT [humans]/lim	5961337
38	#36 NOT #37	212
39	#36 NOT #37 AND [english]/lim	181

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded glucosamine sulfate. 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 pratitioners 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 glucosamine sulfate to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer glucosamine sulfate 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 glucosamine sulfate for the following conditions or disease: (check all that apply)

   - o Degenerative joint disease
   - o Osteoarthritis
   - o Other (please explain) _____

5. I use compounded glucosamine sulfate 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 glucosamine sulfate.
   - o Other (please explain) _____

6. Do you stock non-patient-specific compounded glucosamine sulfate at your practice?

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

7. I obtain compounded glucosamine sulfate 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.