Summary Report

Niacin

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

Apo	Apolipoprotein
API	Active Pharmaceutical Ingredient
CVD	Cardiovascular disease
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FFA	Free fatty acids
HDL	High-density lipoproteins
IRB	Institutional Review Board
LDL	Low-density lipoproteins
NaCl	Sodium chloride
OTC	Over-the-counter
PPARγ	Peroxisome proliferator-activated receptor γ
ROA	Route of administration
SME	Subject matter expert
TG	Triglyceride
UK	United Kingdom
US	United States
VLDL	Very-low-density lipoproteins

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of niacin (UNII code: 2679MF687A), 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 niacin 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 niacin 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 niacin 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

Niacin was nominated for inclusion on the 503B Bulks List by Fagron for hyperlipidemia via a 50-300 mg injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of niacin.[6-10]

The reason provided for nomination to the 503B Bulks List was some studies have indicated that intravenous niacin can lead to better outcomes in controlling hyperlipidemia.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of niacin 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 niacin; name variations of niacin 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 niacin. 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: niacin, injectable administration, and therapeutic use for hyperlipidemia (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 8, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 8, 2020 for clinical practice guidelines that recommended the use of niacin and provided sufficient information on dosing and administration.

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 niacin 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 niacin 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 niacin 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 niacin; setting; total number of patients; number of patients who received niacin; patient population; indication for use of niacin; dosage form and strength; dose; ROA; frequency and duration of therapy; use of niacin in a combination product; use and formulation of niacin in a compounded product; use of niacin 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 niacin was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use niacin: cardiology, endocrinology, 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 niacin 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

- Niacin is not available as an FDA-approved product in the nominated dosage form and ROA. Niacin is available as FDA-approved oral prescription products.
- Niacin is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for niacin.
- Niacin is not available in the nominated dosage form and ROA in any of the foreign registries searched.

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 391 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 304 titles and abstracts were screened. After screening, the full text of 46 articles was reviewed. Finally, 4 studies were included. Forty-two studies were excluded for the following reasons: wrong dosage form or ROA (14 studies); niacin only mentioned briefly (11); niacin not used clinically (9); wrong study design (8).

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

Characteristics of included studies

The 4 included studies were published between 1986 and 2012. There were 2 experimental studies, 0 observational studies, 2 descriptive studies, and 0 clinical practice guidelines. The 4 studies were conducted in the following countries: Russia and US.

A total of 113 patients participated in the 4 included studies. The number of patients in each study ranged from 1 to 100.

Outcome measures differed among the included studies and included: number of angina pectoris attacks, atherogenic index, glucose levels, insulin levels, plasma free fatty acids (FFA) concentration, triglyceride (TG) levels, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and total cholesterol.

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

Use of niacin

One patient received niacin 250 mg/day as a treatment for hypertriglyceridemia. The dosage form, ROA, and duration of treatment were not specified.

Eleven patients received niacin 285 mg as an experimental treatment to suppress lipolysis and reduce fatty acid spillover, administered once intravenously.

Fifty patients received niacin 1.5 g/day for 6 months as a comparator treatment for type IIb hyperlipoproteinemia and ischemic heart disease. The dosage form and ROA were not specified.

One patient received niacin 1.5 g/day as a treatment for heparin-induced hyperlipidemia. The dosage form, ROA, and duration of treatment were not specified.

Refer to Tables 6 and 7 for summaries of dosage by indication.

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

In 1 study, the authors' concluding statement suggested that the use of intravenous niacin provided additional lipolysis suppression and reduction in fatty acid spillover.[10] In 1 study, the authors' concluded that the use of niacin was not preferred for hyperlipoproteinemia IIb.[11] Another study concluded that niacin along with fibrates and insulin can be considered for rapid reduction of TG.[12] One study's concluding statement did not address the use of niacin.[13] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 4 included studies, 6 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of niacin.

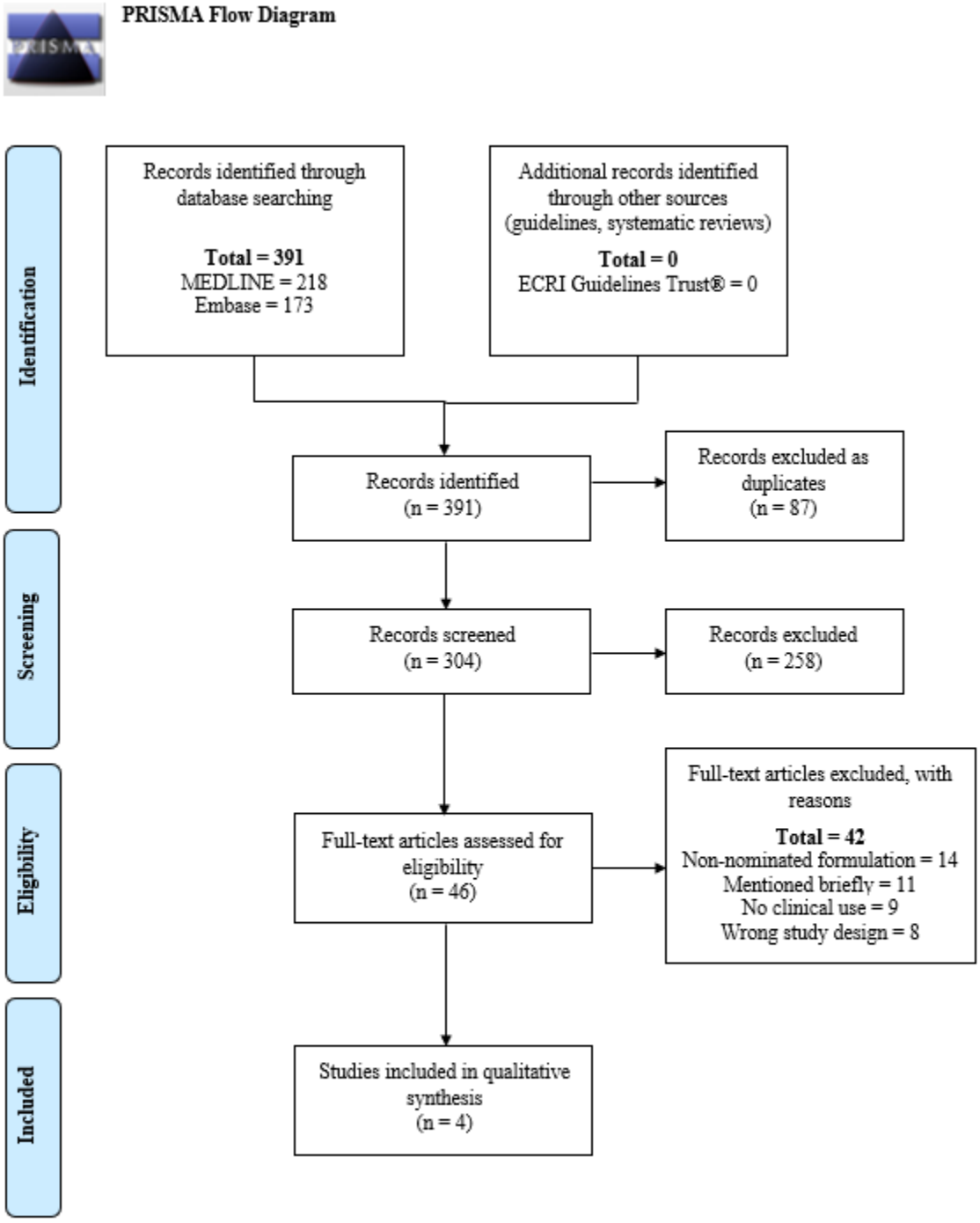
Niacin (also known as vitamin B3) has been used since 1955 and is available in two chemical forms, nicotinic acid and nicotinamide.[14] For hyperlipoproteinemia or peripheral vascular disease, only nicotinic acid is used.[14] For nutritional supplementation or pellagra, both nicotinic acid and nicotinamide are used.[14] Although niacin has been around for many years, its mechanism of action for lipid metabolism is still not fully understood.[14] Some proposed mechanism of actions for lipid metabolism include niacin's antilipolytic effect mediated via nicotinic acid receptors, niacin's ability to speed up "intracellular degradation of Apolipoprotein (Apo) B containing lipoproteins such as very-low-density lipoproteins (VLDL) and LDL by inhibiting TG synthesis," and niacin's ability to decrease hepatic TG synthesis via inhibition of diacylglycerol acyltransferase 2.[14] For increasing HDL levels, niacin slows the "degradation of ApoA-I-containing lipoproteins, increases peroxisome proliferator-activated receptor γ (PPARγ) expression and enhances PPARγ transcriptional activity in macrophages."[14] Niacin also downregulates the action of cyclic adenosine monophosphate, thus lowering the FFA levels.[14]

The 2018 American College of Cardiology/American Heart Association guideline on the management of blood cholesterol stated that, niacin is a triglyceride-lowering drug with mild LDL-lowering action, but "[randomized controlled trials] do not support their use as add-on drugs to statin therapy."[15] The guideline did not provide either a dosage form or ROA for niacin.

The use of niacin may be limited by its side effect of flushing, which occurs in 70-80% of patients.[16] The oral extended-release niacin formulation can help reduce flushing.[16]

Few studies used injectable niacin for hyperlipidemia. Three studies evaluated FFA levels in patients who received intravenous niacin.[10,16,17] The first study tested intravenous heparin 50 mg alone, intravenous nicotinic acid 100 mg alone, and both heparin and nicotinic acid in cardiovascular disease patients after a heavy fat meal.[17] The plasma glyceride-glycerol levels were significantly lower after heparin alone and after both heparin and nicotinic acid injection while nicotinic acid alone had no effect on the plasma glyceride-glycerol and FFA levels.[17] The second study looked at TG, FFA, blood glucose, and insulin levels when inhibited by glucose or nicotinic acid in normal subjects compared to those with type IV hyperlipoproteinemia after a high carbohydrate diet.[18] Nicotinic acid did not cause a nocturnal rise of TG levels and the authors concluded that the "effectiveness of nicotinic acid in inhibiting nocturnal lipolysis and preventing carbohydrate-induction of hypertriglyceridemia might have consequences for management of endogenous hypertriglyceridemia."[18] The final study examined the effect of intravenous niacin compared to saline on FFA during continuous feeding in lean and obese patients. Six lean patients and 5 obese patients during continuous feeding received intravenous infusion niacin (2.8 mg/min) on one occasion and saline the other.[10] During the niacin infusion, total FFA concentrations and oleate appearance were lower in both patient types when compared to during the saline infusion.[10] The authors concluded that niacin can provide additional lipolysis suppression during meal absorption and reduce fractional spillover in both normal and obese patients.[10] One case report described a patient in whom self-injection of niacin into his ulnar artery caused pain and severe ischemia with tissue necrosis and gangrene.[19]

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[12,13]	2
Experimental[10,11]	2
Observational	0

Table 4. Number of studies by country

Country	**Number of Studies**
Russia[11]	1
US[10,12,13]	3
	Total US: 3 Total Non-US Countries: 1

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
Henann, 1985, US[13]	Case report	1 Patient (0%, 58 y)	• Nicotinic acid	TG and cholesterol concentrations	Hyperlipidemia in this patient appeared to be induced by heparin. "Further investigation is needed to determine who may be at risk of experiencing this adverse reaction to heparin."
Klimov *et al*, 1995, Russia[11]	–	100 Patients (90%, mean 51.2 ± 1.1 y)	• Nicotinic acid (50) • Lipostabil (50)	LDL cholesterol, HDL cholesterol, total cholesterol, TG, atherogenic index, number of angina pectoris attacks	"Lipostabil is a preferable alternative in the treatment of patients with moderate, dietary noncorrigible hyperlipoproteinemia IIb and ischemic heart disease."
Nelson *et al*, 2012, US[10]	–	11 Patients total Lean subjects (83%, mean 31 ± 3 y) Obese subjects (60%, mean 39 ± 3 y)	• Niacin (11) • Sodium chloride (11) All patients received both niacin and sodium chloride	Plasma FFA concentration, glucose, insulin, TG	Niacin produces additional lipolysis suppression during meal absorption and reduction in fractional spillover compared to saline in both lean and obese patients. "Intravenous niacin provides a model for acutely improving dietary fat storage."
Poonuru *et al*, 2011, US[12]	Case report	1 Patient (100%, 53 y)	• Niacin	TG	The patient's TG levels normalized over one month, and insulin infusion can be considered a safe treatment for "rapid reduction of serum TG in addition to fibrates and niacin."

Abbreviations: "–", not mentioned; FFA, free fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Hypertriglyceridemia[12]	250 mg/day	–	–	–	–
Lipolysis suppression and reduction in fatty acids spillover[10]	285 mg	–	–	Intravenous	Once
Heparin-induced hyperlipidemia[13]	1.5 g/day	500 mg	–	–	–

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Type IIb hyperlipoproteinemia and ischemic heart disease[11]	1.5 g/day	–	–	–	6 months

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combinations

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

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. Twenty-three SMEs discussed niacin. Amongst these 23 SMEs, there were 5 medical doctors, 2 naturopathic doctors, 14 pharmacists, 1 regulatory affairs specialist, and 1 doctor of philosophy. The SMEs specialized and/or were board-certified in cardiology, critical care, naturopathy, nutrition, pediatrics, primary care/family practice, occupational medicine, sterile compounding, and psychiatry, working in academia, academic medical centers, consulting, hospital/health systems, pharmacy/pharma companies, and private practice/clinics. The SMEs had been in practice for 7 to 39 years.

Most SMEs did not think a niacin injection is needed or had not used niacin. A few SMEs commented that oral niacin causes a lot of flushing and the injection form might make it worse. One of the SMEs had only used niacin for lipid abnormalities but because of how poorly tolerated oral niacin was, they do not prescribe it because "no one would keep taking it anyways." One SME expressed that niacin is commercially available in multi-vitamin products and the only time they could envision intravenous niacin being used is if there is a multi-vitamin shortage; however, patients could be given it orally. Another SME specializing in cardiology stated that oral niacin "has been shown to be ineffective in reducing cardiovascular disease (CVD) risk despite appreciable lipid lowering effects." While niacin can be used as an adjunct to statins and other cholesterol lowering medications, its use has been decreasing over the past decade because "2 large randomized controlled studies (AIM-HIGH and HPS2-THRIVE) were completely negative on CVD outcomes."[20-25] On the contrary, one SME stated they could see the usefulness of having the injection formulation if it can be given at a lower dose and/or mixed with other substances to mitigate the vasomotor side effects. Niacin is a safe and "fabulous drug for cholesterol" but has horrible side effects (i.e. flushing, dizziness, headaches). A pharmacy mentioned that they compounded niacin in the past; however, they "have changed based on regulation and updates" and "[do not] compound [niacin] for [503B]." They did not specify the dosage form and ROA that they had compounded.

For niacin deficiency, several SMEs always use oral first before considering parenteral. One SME stated that a scenario in which parenteral niacin could be considered is for surgery patients who have short bowel syndrome. Even though the patient may have an intact jejunum, the motility might be too fast, so the nutrients do not have enough contact time to be absorbed. Other indications mentioned by SMEs included a few scattered reports for niacin use in migraine headaches while another had looked into how to formulate niacin for methanol toxicity. One SME also mentioned that niacin and niacinamide act as dopamine reuptake promotors, which can help certain patients with schizophrenia.

Several SMEs addressed the use of B vitamins in general. One SME stated that children with inborn errors in metabolism need additional B vitamins so they use what they can get, mostly focusing on thiamine, folic acid, and vitamin B12. Another SME commented if they wanted a vitamin via the IV route, they would probably want thiamine, pyridoxine, and cyanocobalamin available. Another SME always gives vitamin C with vitamin B complex, magnesium, and sometimes other minerals. B vitamins have also been mentioned being used in a Myers' cocktail, which is usually made with calcium, magnesium, vitamin C, and trace minerals.

Summary of survey results

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 niacin prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded niacin

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded niacin

No respondents to survey distributed via professional medical associations

CONCLUSION

Niacin was nominated for inclusion on the 503B Bulks List for hyperlipidemia via a 50-300 mg injection. Niacin is not available in the nominated dosage form and ROA in any of the national medical registries searched.

In the articles included from the literature review, niacin was used for various indications related to cholesterol, lipids, and CVD. One study identified used niacin intravenously for lipolysis suppression and reduction in fatty acids spillover. The 2018 American College of Cardiology/American Heart Association guideline on the management of blood cholesterol stated that, "niacin may be useful in some patients with severe hypertriglyceridemia, but research doesn't support their use as add-on drugs to statin therapy."[15]

From the interviews conducted, most SMEs did not think an injection formulation is needed or had not used niacin. Oral niacin causes flushing and is poorly tolerated so the injection form might make this worse. Another SME stated that oral niacin "has been shown to be ineffective in reducing CVD risk despite appreciable lipid lowering effects." On the other hand, a SME stated the injection formulation could be useful if it is given at a lower dose and/or mixed with other substances to mitigate the vasomotor side effects. For niacin deficiency, several SMEs used the oral formulation first before considering parenteral with one SME commenting that parenteral niacin could be considered is for surgery patients who have short bowel syndrome. Another SME expressed that the only time they could envision intravenous niacin being used is if there is a multi-vitamin shortage; however, patients could be given oral niacin and hopefully have absorption of it. A pharmacy also mentioned that they compounded niacin in the past but no longer do so due to changes in regulations and updates; they did not specify the dosage form and ROA.

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 March 6, 2020
- Date last searched: March 8, 2020
- Limits: Humans (search hedge); English language
- Number of results: 218

1	niacin/	10721
2	niacin$.tw.	5270
3	nicamin$.tw.	1
4	(nicotin$ adj2 acid$).tw.	6326
5	nicotinate.tw.	1322
6	ni#otinsaure.tw.	0
7	(antipellagra$ adj2 vitamin$).tw.	5
8	(anti pellagra$ adj2 vitamin$).tw.	1
9	(vitamin$ adj2 b3).tw.	426
10	or/1-9	18761
11	exp administration, intravenous/	141866
12	infusions, parenteral/	26196
13	infusions, subcutaneous/	1049
14	injections/	42200
15	injections, intramuscular/	30794
16	injections, subcutaneous/	32433
17	inject$.tw.	728574
18	infusion$.tw.	241859
19	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12013
20	subcutaneous$.tw.	162832

21	intravenous$.tw.	335064
22	intra venous$.tw.	568
23	intravascular$.tw.	46962
24	intra vascular$.tw.	296
25	intramuscular$.tw.	51528
26	intra muscular$.tw.	709
27	or/11-26	1396935
28	exp hyperlipidemias/	65419
29	hartnup disease/	249
30	de.fs.	2949891
31	dt.fs.	2184738
32	ad.fs.	1393722
33	tu.fs.	2191668
34	hyperlipid?em$.tw.	30032
35	hyperlip?em$.tw.	2976
36	lipid?em$.tw.	748
37	lip?em$.tw.	2976
38	hyperlipoprotein?em$.tw.	4494
39	hypercholesterol?em$.tw.	33981
40	hypercholester?em$.tw.	878
41	hypercholesterin?em$.tw.	199
42	cholesterol?em$.tw.	1364
43	cholester?em$.tw.	85
44	cholesterin?em$.tw.	41
45	hypertriglycerid?em$.tw.	13778
46	triglycerid?em$.tw.	737

47	hartnup.tw.	152
48	(neutral amino acid$ adj3 (defect$ or disorder$)).tw.	6
49	or/28-48	5715920
50	and/10,27,49	581
51	exp animals/ not humans/	4675662
52	50 not 51	292
53	limit 52 to english language	218

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 8, 2020
- Limits: Humans (search hedge); English language
- Number of results: 173
- Notes: Tested with Emtree term 'nicotinic acid' as major focus and not; additional results not relevant.

1	nicotinic acid'/mj	10857
2	niacin*':ti,ab,tn	7653
3	nicamin*':ti,ab,tn	4
4	(nicotin* NEAR/2 acid*):ti,ab,tn	10074
5	nicotinate':ti,ab,tn	1834
6	nicotinsaure':ti,ab,tn	5
7	nikotinsaure':ti,ab,tn	4
8	(antipellagra NEAR/2 vitamin*):ti,ab,tn	8
9	anti:ti,ab,tn AND ((pellagra NEAR/2 vitamin*):ti,ab,tn)	7
10	(vitamin* NEAR/2 b3):ti,ab,tn	506
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	23774
12	parenteral drug administration'/de	2103
13	intramuscular drug administration'/de	71558
14	intravenous drug administration'/exp	391902
15	subcutaneous drug administration'/de	100774
16	injection'/exp	247453
17	inject*':ti,ab	1082000
18	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18105
19	subcutaneous*':ti,ab	245757
20	intravenous*':ti,ab	482508
21	intra venous*':ti,ab	1434

22	intravascular*':ti,ab	67454
23	intra vascular*':ti,ab	675
24	intramuscular*':ti,ab	74342
25	intra muscular*':ti,ab	1269
26	#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 OR #25	2040993
27	drug dose':lnk	621819
28	drug administration':lnk	1718631
29	drug therapy':lnk	3843836
30	hyperlipidemia'/exp	163035
31	hartnup disease'/de	397
32	hyperlipid$em*':ti,ab	48716
33	hyperlip$em*':ti,ab	5025
34	lipid$em*':ti,ab	1616
35	lip$em*':ti,ab	4835
36	hyperlipoprotein$em*':ti,ab	5970
37	hypercholesterol$em*':ti,ab	49819
38	hypercholester$em*':ti,ab	1402
39	hypercholesterin$em*':ti,ab	406
40	cholesterol$em*':ti,ab	2262
41	cholester$em*':ti,ab	135
42	cholesterin$em*':ti,ab	57
43	hypertriglycerid$em*':ti,ab	19831
44	triglycerid$em*':ti,ab	1154
45	hartnup':ti,ab	277
46	('neutral amino acid*' NEAR/2 (defect* OR disorder*)):ti,ab	4
47	#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #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	4652101

48	#11 AND #26 AND #47	358
49	[animals]/lim NOT [humans]/lim	6001338
50	#48 NOT #49	217
51	#48 NOT #49 AND [english]/lim	173

Appendix 2. Survey instrument for professional medical associations

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

   - o Yes
   - o No

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

   - o Injection
   - o None of the above

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

   - o Hyperlipidemia
   - o Other (please explain) _____

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

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

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

7. I obtain compounded niacin 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.