Summary Report

Niacinamide

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
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 niacinamide (UNII code: 25X51I8RD4), 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 niacinamide 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 niacinamide 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 niacinamide and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Niacinamide was nominated for inclusion on the 503B Bulks List by Alliance for Natural Health USA, American Association of Naturopathic Physicians, Integrative Medicine Consortium, McGuff Compounding Pharmacy Services, Fagron, and the Outsourcing Facilities Association. Niacinamide was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Niacinamide was nominated as a 100 mg/mL or 100 mg/37 mL intravenous and intramuscular injection for pellagra, energy and immune boost, atherosclerosis, hyperlipoproteinemia, hypertriglyceridemia, myocardial infarction prophylaxis, nutritional supplementation, peripheral vascular disease, tinnitus, dementia, Alzheimer's disease, carcinoid syndrome, and Hartnup's disease.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of niacinamide.[6-22]

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

- There is no single-agent, FDA-approved injectable form of niacinamide.
- Niacinamide is preferred over niacin to treat pellagra because niacin can cause flushing and/or pruritus. Since pellagra does have dermatological manifestation, the flush reaction and pruritus can complicate treatment.
- Currently, only oral niacinamide products exist and may cause nausea in patients with severe pellagra who require high doses of niacinamide. Intravenous or intramuscular administration requires a lower dose so a compounded injectable can help patients with severe pellagra avoid nausea.
- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Niacinamide is commonly used in the Myers' cocktail to provide an immune boost for patients. The Myers' cocktail contains many ingredients and poses a safety risk when a prescriber must mix this in office.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of niacinamide 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 niacinamide; name variations of niacinamide 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 niacinamide. 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: niacinamide, intravenous or intramuscular administration, and therapeutic use for pellagra or other conditions (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 April 1, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on April 1, 2020 for clinical practice guidelines that recommended the use of niacinamide 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 niacinamide 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 niacinamide 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 niacinamide 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 niacinamide; setting; total number of patients; number of patients who received niacinamide; patient population; indication for use of niacinamide; dosage form and strength; dose; ROA; frequency and duration of therapy; use of niacinamide in a combination product; use and formulation of niacinamide in a compounded product; use of niacinamide 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 niacinamide was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use niacinamide: cardiology, endocrinology, naturopathy, neurology, nutrition, oncology, otolaryngology, 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 niacinamide 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

- Niacinamide is not available as an FDA-approved single-agent injectable product or in the nominated combination. Niacinamide is available as FDA-approved injectable products in combination with additional API.
- Niacinamide is not available as an OTC product in the US in the nominated dosage form and ROA.
- There is a current United States Pharmacopeia (USP) monograph for niacinamide.
- Niacinamide is available in the nominated dosage form and ROA in Australia.

Table 1. Currently approved products – US

No approved single-agent injectable products or nominated combination in the US

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Nicotinamide / Dexpanthenol / Pyridoxine hydrochloride / Riboflavine sodium phosphate / Thiamine hydrochloride	50 mg/mL / 10 mg/mL / 25 mg/mL / 2.5 mg/mL / 5 mg/mL	Solution	Injection	Australia	Schedule 4	10/8/1991

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

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 1289 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1109 titles and abstracts were screened. After screening, the full text of 100 articles was reviewed. Finally, 2 studies were included. Ninety-eight studies were excluded for the following reasons: wrong study design (72 studies); niacinamide not used clinically (7); wrong indication (7); wrong substance (4); niacinamide used as brand or proprietary product (4); wrong dosage form or ROA (2); language other than English (1); unable to obtain (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 1950 and 1972. There were 0 experimental studies, 1 observational study, 1 descriptive study, and 0 clinical practice guidelines. Both studies were conducted in US.

A total of 26 patients participated in the 2 included studies. The number of patients in each study was 1 and 25.

The outcome measures in the included studies were improvement of lingual abnormalities and improvement in clinical signs of carcinoid syndrome complicated by pellagrous dermatitis.

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

Use of niacinamide

Nine patients received niacinamide as an experimental treatment for niacin deficiency (pellagra) in pulmonary tuberculosis, administered intravenously as a 500 mg/day dose.[23,24]

Refer to Table 6 for summary of dosage by indication.

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

In 1 study, the authors' conclusion stated that the oral and parenteral administration of niacinamide led to rapid improvement of pellagrous dermatitis.[24] In the other study, the authors' concluded that B vitamins should be administered together as these are the most commonly encountered vitamin deficiencies and their function is interrelated.[23] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

Six studies were identified that provided valuable information about the pharmacology and historical use of niacinamide.

Niacinamide, also known as nicotinamide, is an active form of vitamin B3 (niacin). Niacin is a water-soluble vitamin that is converted to nicotinamide adenine dinucleotide (NAD) and reduced nicotinamide adenine diducleotide (NADH).[25] Pellagra is a deficiency in tissue niacin that manifests as a dermatitis characterized as a "striking, symmetrical, well-defined photosensitivity".[25] Pellagra may also be associated with gastrointestinal, neurological and psychological signs.[25,26] The World

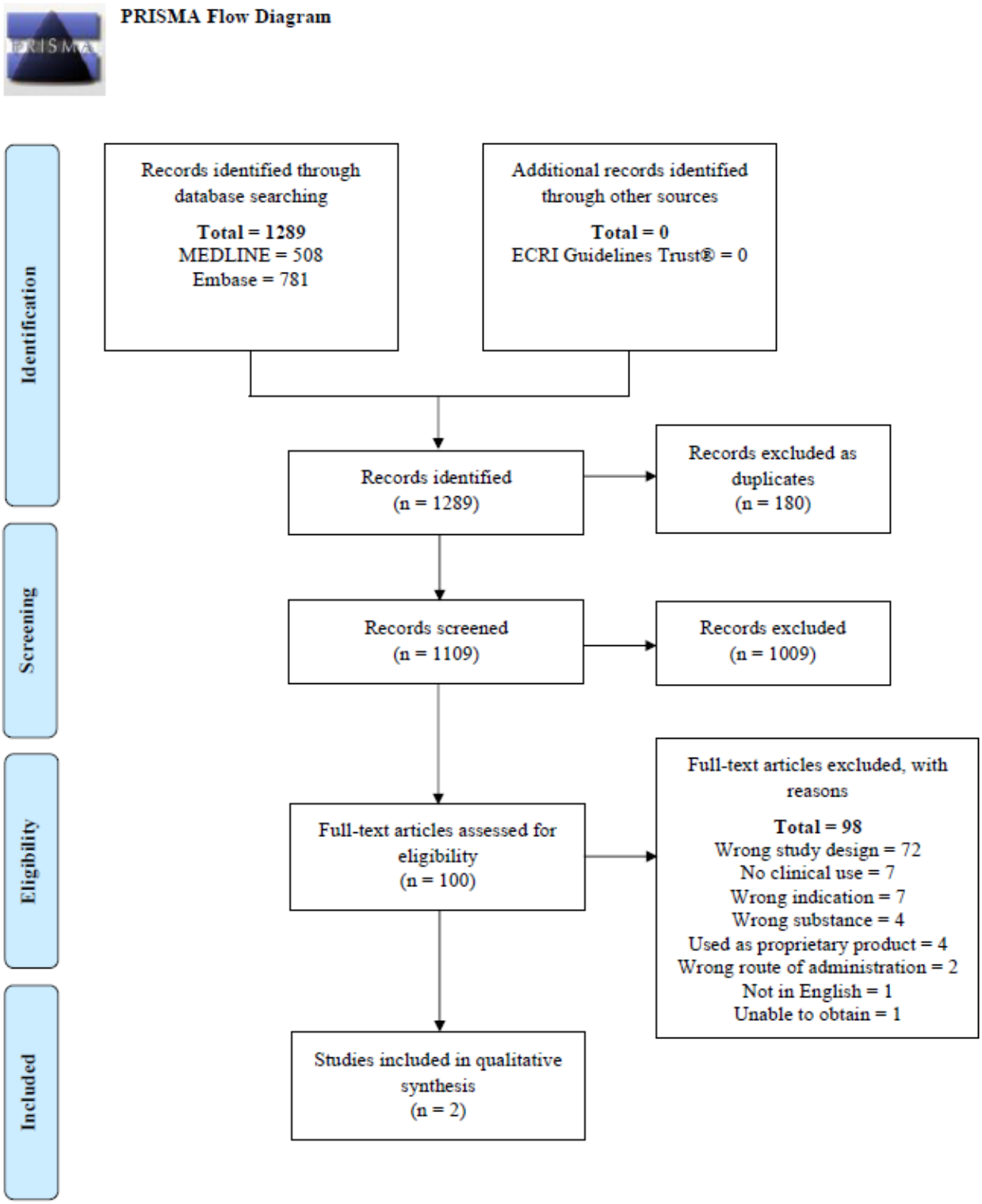
Health Organization recommends that pellagra be treated with nicotinamide 300 mg daily in divided doses for 3-4 weeks.[26] Therapeutic doses of niacin are provided as nicotinamide because this substance is not associated with the side effects that occur with administration of niacin and nicotinic acid, such as flushing and urticaria; in particular nicotinamide is not a vasodilator and therefore rarely causes cutaneous flushing.[13,26] Mild headaches and dizziness have been reported with parenteral administration of nicotinamide.[13] Oral nicotinamide is unpalatable in solution and is usually provided as capsules or tablets.[13] Large oral doses of nicotinamide (up to 3 g/day for up to 5 years) have been administered to patients with schizophrenia, skin conditions such as pemphigoid, and type I diabetes mellitus with few sides effects.[13,27] However, the authors of a review on the use of high-dose nicotinamide cautioned that higher doses of this substance "should still be considered as having toxic potential."[13]

Primary pellagra occurs due to inadequate dietary intake of niacin or tryptophan (tryptophan is a precursor for niacin).[25] The prevalence of primary pellagra in the US is low; according to Castiello et al, "improved nutrition in the US has made primary dietary niacin deficiency so unusual that clinical recognition of pellagra should alert the physician to the possibility that the patient has an underlying disease."[24] Secondary pellagra occurs due to defective absorption or utilization of niacin.[25] Underlying etiologies of secondary pellagra include: conditions that cause malasbsorption, such as inflammatory bowel disease, Crohn's disease, major gastrointestinal surgery or chronic alcoholism; use of certain drugs, such as isoniazid, 6-mercaptopurine, 5-fluorouracil or azathioprine; or conditions that disrupt metabolic pathways that involve niacin, such as carcinoid syndrome.[25]

One of the disease states in which secondary pellagra can develop is carcinoid syndrome in patients with carcinoid tumors. Carcinoid tumors are abnormal growths of secretory cells in the intestinal and bronchial submucosa. According to Castiello et al, approximately 5% of patients with carcinoid tumor develop malignant or productive carcinoid syndrome.[24] One of the possible cutaneous manifestations of malignant carcinoid syndrome is pellagrous dermatitis.[24] In carcinoid syndrome, patients generate 5-hydroxytryptamine (serotonin) from tryptophan.[25] In a healthy person, tryptophan is a precursor for niacin and serotonin, with only 1% of tryptophan metabolized to serotonin.[24] However, in carcinoid syndrome, as much as 60-99% of tryptophan can be used to produce serotonin, which results in relative underproduction of niacin.[24,25] With already low tissue niacin level, diminished niacin and tryptophan intake can cause pellagra to develop.[24]

Niacinamide was nominated for use in the Myers' cocktail. The Myers' cocktail was developed by the late Dr. John Myers for treatment of a variety of medical conditions. The exact formulation of the cocktail is unknown as "no published or written material on the treatment was available."[28] It should also be noted that even the originator, Dr. Myers, did not make the cocktail the same way each time. Two randomized control trials from 1999 and 2009 used the Myers' cocktail for various acute and chronic conditions and fibromyalgia, respectively.[7,29] Only one of the studies used a formulation of Myers' cocktail in which niacinamide was included.[7] The formulation in this study included 100 mg of niacinamide, along with magnesium chloride hexahydrate, calcium gluconate, hydroxocobalamin, pyridoxine hydrochloride, dexpanthenol, thiamine hydrochloride, riboflavin, panthenol, and vitamin C.[7] The authors found that while most patients experienced relief for fibromyalgia compared to baseline, there was no statistically significant difference between patients who received the Myers' cocktail and those who received the placebo, so the efficacy is still uncertain.[7]

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[24]	1
Experimental	0
Observational[23]	1

Table 4. Number of studies by country

Country	**Number of Studies**
US[23,24]	2
	Total US: 2 Total Non-US Countries: 0

Table 5. Summary of included studies

Indication 1: Niacin deficiency (pellagra)					
Author, Year, Country	**Study Type[a]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Castiello *et al.*, 1972, US[24]	Case report	63-year-old woman with carcinoid syndrome and secondary niacin deficiency	• Oral and parenteral niacinamide (1)	Improvement in clinical signs of carcinoid syndrome complicated by pellagrous dermatitis	"In our patient, oral and parenteral administration of niacinamide led to rapid clearing of the pellagrous dermatitis."
Sevringhaus *et al.*, 1950, US[23]	–	25 Patients with pulmonary tuberculosis and secondary niacin deficiency (sex, age not provided)	• Treated group (14): oral and/or intravenous (8) nicotinamide • Control group (11): placebo pills	Improvement in lingual abnormalities	"At the end of the therapy, the overall evaluation showed lingual improvement in 6 patients, consisting chiefly of reduction in redness and swelling and papillary regeneration. There was no change in 2 patients and progression of glossitis in 5 patients. In the control population, 5 patients revealed improvement in the glossitis comparable to the treated patients, 2 showed no improvement, and in 2 the condition became worse."

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

Table 6. Dosage by indication – US

Indication	**Dose**	**Concentration**	**Dosage Form**	**Route of Administration**	**Duration of Treatment**
Niacin deficiency[23,24]	500 mg/day	–	Solution	Intravenous	28-56 days

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Niacinamide 100 mg in 37 mL for Myers' cocktail	0
	Niacinamide 100 mg/mL / Dexpanthenol 2 mg/mL / Pyridoxine HCL 2 mg/mL / Riboflavin-5'-phosphate sodium 2 mg/mL / Thiamine HCl 100 mg/mL	0

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. Twenty SMEs discussed niacinamide. Amongst these 20 SMEs, there were 5 medical doctors, 1 naturopathic doctor, 12 pharmacists, 1 nurse practitioner, and 1 doctor of philosophy. The SMEs specialized and/or were board-certified in cardiology, dermatology, naturopathy, nutrition, oncology/hematology, primary care and family medicine, and psychiatry, working in academic medical practice, consulting, hospital, pharmacy/pharma company, and private practice/clinic. The SMEs had been in practice for 7 to 40 years.

Most of the SMEs had not used niacinamide and did not see the need for an injectable formulation. One SME said niacinamide is "pretty much the same" as niacin and did not understand why it would be needed for patients on long-term intravenous nutrition. The SMEs generally preferred an oral formulation, although one SME said "niacinamide is the normal B3 used for parenteral use" and another mentioned that people use it topically as it raises skin pH "to make more collagen and achieve youthful [skin] appearance."

Two SMEs stated that niacinamide can be used for pellagra (vitamin B3 deficiency), however they differed in the route in which it should be administered; one SME stated that is generally used orally while the other stated that it is administered parenterally in the office. According to one SME, a classic presentation of pellagra is an alcoholic with a poor diet, which leads to profound vitamin deficiency that manifests as a photo-sensitive skin eruption. This SME stated, "most of the niacinamide available now is in [manufactured] B complex solutions." If someone needed more vitamin B3, then they would add it to an existing formula, noting that a 503A pharmacy can make this. One SME stated that because there are a lot of products that contain niacinamide, there are not any concerns with safety.

Two SMEs discussed carcinoid syndrome. One SME does not use niacinamide but uses octreotide injections for carcinoid syndrome, which is given 3 times a day and most patients have to be admitted during the treatment. Due to its frequent administration, the SME stated that if there is another treatment that can be given less frequently, like once a day or once a week, then it would be beneficial. Another SME was not in favor of niacinamide used as an injection but could see some value for it in Alzheimer's disease or carcinoid syndrome. The SME did not see the value in combination products because they do not like pre-fixed dosing and would prefer custom dosing.

One SME was able to provide background information on the Myers' cocktail. The SME stated that it originated in Baltimore, Maryland by Dr. Myers. It is a combination that typically includes calcium, magnesium, trace minerals, B vitamins, and vitamin C used for patients who have difficulty recovering from an acute infection or for people with chronic fatigue. It was previously used for people with chronic hepatitis C before there was an effective therapy for it.

One SME talked about the use of niacinamide in psychiatry. According to this SME, niacinamide acts as a dopamine reuptake promotor, so it can be helpful for under-methylated (low dopamine level) people but can harm over-methylated patients because they have excessive activity at dopamine receptors. The SME stated that it can help certain patients with schizophrenia.

For use of niacinamide in hyperlipidemia, one SME stated that they are unaware of hypolipidemic activity in niacinamide.

Results of survey

Zero people responded to the surveys 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 niacinamide prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded niacinamide

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

CONCLUSION

Niacinamide was nominated for inclusion on the 503B Bulks List as an intravenous and intramuscular injection to treat pellagra, energy and immune boost, atherosclerosis, hyperlipoproteinemia, hypertriglyceridemia, myocardial infarction prophylaxis, nutritional supplementation, peripheral vascular disease, tinnitus, dementia, Alzheimer's disease, carcinoid syndrome, and Hartnup's disease. Niacinamide is available in the nominated dosage form and ROA in Australia.

From the literature review and interviews conducted, niacinamide is used for pellagra. However, most of the interviewed SMEs had not used niacinamide and did not see the need for its use as an injection. One SME stated that if it were to be used parenterally for pellagra, then it would be used in the office. For carcinoid syndrome, SMEs had not used niacinamide but thought there could be some value to it.

Zero people responded to the surveys 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 31, 2020
- Date last searched: April 1, 2020
- Limits: Humans (search hedge); English language
- Number of results: 508

1	niacinamide/	12367
2	amid$ pp.tw.	4
3	nicotinamid$.tw.	20785
4	niacetamid$.tw.	0
5	niacinamid$.tw.	489
6	niacin amid$.tw.	3
7	nicamid$.tw.	0
8	nicosedin$.tw.	0
9	nicotamid$.tw.	10
10	(nicotinic adj2 amid$).tw.	92
11	nicotinoylamid$.tw.	1
12	ni#otinsaureamid$.tw.	0
13	nikotamin$.tw.	0
14	vitamin$ b3.tw.	380
15	vitamin$ b 3.tw.	53
16	vitamin$ pp.tw.	136
17	or/1-16	29663
18	exp administration, intravenous/	142076
19	infusions, parenteral/	26202
20	injections/	42264

21	injections, intramuscular/	30826
22	inject$.tw.	730829
23	infusion$.tw.	242372
24	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12042
25	intravenous$.tw.	336049
26	intra venous$.tw.	571
27	intravascular$.tw.	47065
28	intra vascular$.tw.	297
29	intramuscular$.tw.	51709
30	intra muscular$.tw.	709
31	or/18-30	1294100
32	pellagra/	1129
33	drug therapy/	30402
34	ad.fs.	1397385
35	dt.fs.	2191450
36	tu.fs.	2197147
37	pc.fs.	1267863
38	pellagr$.tw.	1171
39	((vitamin$ b or vitamin b3 or vitamin$ pp) adj3 deficien$).tw.	1382
40	((italian or lombardy) adj2 lepros$).tw.	1
41	maidism.tw.	0
42	treat$.tw.	5381901
43	therap$.tw.	2718884
44	prevent$.tw.	1386556
45	prophyl$.tw.	161885
46	or/32-45	9450753

47	and/17,31,46	1483
48	exp animals/ not humans/	4685189
49	47 not 48	595
50	limit 49 to english language	508

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 1, 2020
- Limits: Humans (search hedge); English language
- Number of results: 781

1	nicotinamide'/exp	16092
2	amid* pp':ti,ab,tn	7
3	nicotinamid*':ti,ab,tn	25231
4	niacetamid*':ti,ab,tn	0
5	niacinamid*':ti,ab,tn OR 'niacin amid*':ti,ab,tn	785
6	nicamid*':ti,ab,tn	1
7	nicosedin*':ti,ab,tn	0
8	nicotamid*':ti,ab,tn	26
9	(nicotinic NEAR/2 acid*):ti,ab,tn	9528
10	nicotinoylamid*':ti,ab,tn	2
11	nicotinsaureamid*':ti,ab,tn	6
12	nikotinsaureamid*':ti,ab,tn	2
13	nikotamin*':ti,ab,tn	0
14	vitamin* b3':ti,ab,tn	460
15	vitamin* b 3':ti,ab,tn	18
16	vitamin* pp':ti,ab,tn	295
17	#1 OR #2 OR #3 OR #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	41763
18	parenteral drug administration'/de	2118
19	intramuscular drug administration'/de	71583
20	intravenous drug administration'/exp	392141
21	injection'/exp	247461
22	inject*':ti,ab	1084763

23	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18133
24	infusion*':ti,ab	353231
25	intravenous*':ti,ab	483065
26	intra venous*':ti,ab	1437
27	intravascular*':ti,ab	67194
28	intra vascular*':ti,ab	678
29	intramuscular*':ti,ab	73663
30	intra muscular*':ti,ab	1272
31	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	2056539
32	pellagra'/de	2221
33	drug therapy'/de	718253
34	drug dose':lnk	622387
35	drug administration':lnk	1723970
36	drug therapy':lnk	3855526
37	prevention':lnk	1162151
38	pellagr*':ti,ab	1806
39	(('vitamin* b' OR 'vitamin* b3' OR 'vitamin* pp') NEAR/3 deficien*):ti,ab	1838
40	((italian OR lombardy) NEAR/2 lepros*):ti,ab	2
41	maidism':ti,ab	0
42	treat*':ti,ab	7802603
43	therap*':ti,ab	4094896
44	prevent*':ti,ab	1884917
45	prophyl*':ti,ab	258419
46	#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	13076338
47	#17 AND #31 AND #46	2495
48	[animals]/lim NOT [humans]/lim	6012083

49	#47 NOT #48	1109
50	#47 NOT #48 AND [english]/lim	781

Appendix 2. Survey instrument for use of niacinamide

Welcome. We want to understand your clinical use of compounded niacinamide. 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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer niacinamide to your patients?

   - Yes
   - No

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

   - Alzheimer's disease
   - Atherosclerosis
   - Carcinoid syndrome
   - Dementia
   - Energy and immune boost
   - Hartnup's disease
   - Hyperlipoproteinemia
   - Hypertriglyceridemia
   - Myocardial infarction prophylaxis
   - Nutritional supplementation
   - Pellagra
   - Peripheral vascular disease
   - Tinnitus
   - Other (please explain) _____

4. I used niacinamide with my patients as the following: (check all that apply)

    - o FDA-approved drug product
    - o Compounded drug product
    - o Over-the-counter drug product
    - o Dietary supplement (e.g. vitamin or herbal supplement sold in retail)
    - o Other (please explain) _____

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

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

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

7. I obtain compounded niacinamide 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)

    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)

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.