Summary Report

Lysine Hydrochloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

February 2020

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

Table of Tables

REVIEW OF NOMINATIONS

Lysine hydrochloride (Lysine HCl; UNII code: JNJ23Q2COM) and L-lysine (UNII code: K3Z4F929H6) were nominated for inclusion on the 503B Bulks List by AnazaoHealth Corporation, Empower Pharmacy, and the Outsourcing Facilities Association (OFA).

While the exact medical condition in which the compounded product is being requested may not be known, lysine HCl may be used to correct lysine deficiency with or without lysinuric protein intolerance as well as prophylaxis and acute treatment of herpes simplex outbreak. Lysine HCl was also nominated for use in osteoporosis, muscle recovery, prevention of mucositis, and reduction of radiolabeled peptides during peptide receptor radionuclide therapy. Additionally, lysine HCl was nominated for use in combination with L-arginine for use post-LUTATHERA treatment, refer to Table 7 for the nominated formulation. Lysine was nominated for use via a 7-10% topical cream and ointment, 100-500mg oral capsules and solutions, and 25-100mg/mL intravenous or intramuscular solutions for injection.

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

- While there are FDA-approved drug products to treat herpes simplex, certain patient populations may not be adequately managed with approved products alone.
- There are no FDA-approved drug products that contain lysine HCl.
- A patient may need a prescribed dosage form or strength that is not commercially available.
- Possible patient sensitivities to manufactured product dyes, fillers, preservatives and other excipients.
- Manufacturer backorders
- Patients respond differently and the compounded product may be the only product to effectively treat the indication for which it is intended to treat.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of lysine HCl 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 lysine HCl; name variations of lysine HCl 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(s); 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 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing lysine HCl. 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

Two databases (PubMed and Embase) were searched including any date through February 26, 2019. The search included a combination of ("l-lysine"[TIAB] OR "lysine HCl"[TIAB] OR "lysine hydrochloride"[TIAB] OR "lysine monohydrochloride"[TIAB] AND (clinical[TIAB] OR treatment[TIAB] OR therapeutic*[TIAB] OR therapy[TIAB] OR herpes[TIAB] OR deficien*[TIAB] OR intolerance[TIAB] OR virus[TIAB] OR infection[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Upon receipt of new nominations for substances for which a literature review had already been conducted, additional search strategies were constructed for dosage forms, ROA, and/or indications that were not captured in the original searches. A medical librarian constructed comprehensive search strategies for PubMed and Embase. Two search strategies were designed for each database in order to capture the distinct indications in the new nominations (see Appendix 1 for complete search strategies). The first search strategy used a combination of controlled vocabulary terms and keywords to describe three concepts: lysine HCl; muscle recovery; and therapeutic use. The second search strategy also used controlled vocabulary terms and keywords to describe three concepts: lysine HCl; peptide receptor radionuclide therapy; and therapeutic use. Results were limited to original research articles or conference abstracts in English language. All searches were conducted on July 22, 2019. Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence for screening.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of lysine HCl or the implementation of lysine HCl in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

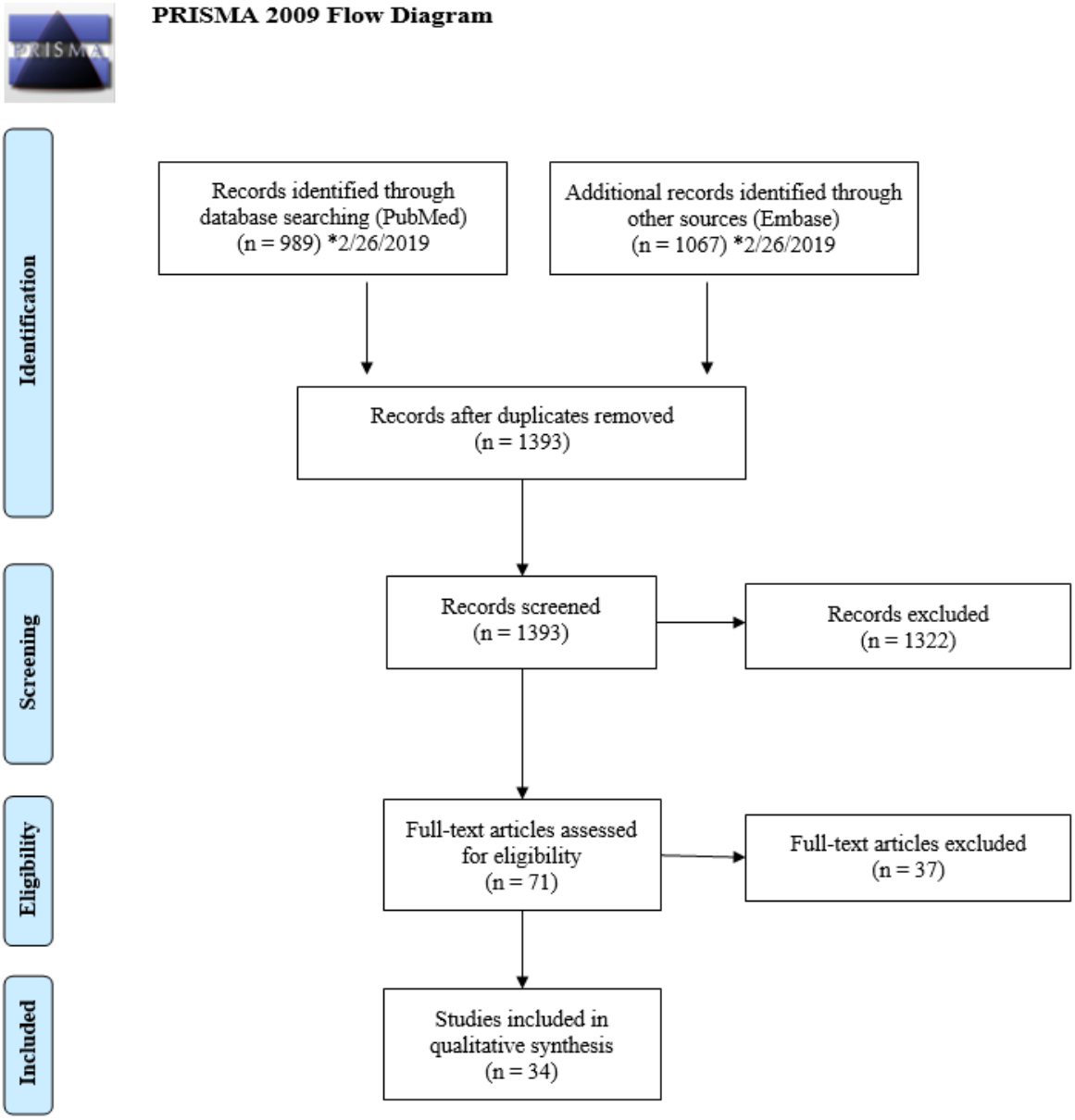
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for lysine HCl use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of lysine HCl compared to alternative therapies.

Results

Please refer to Figure 1 and Figure 2.

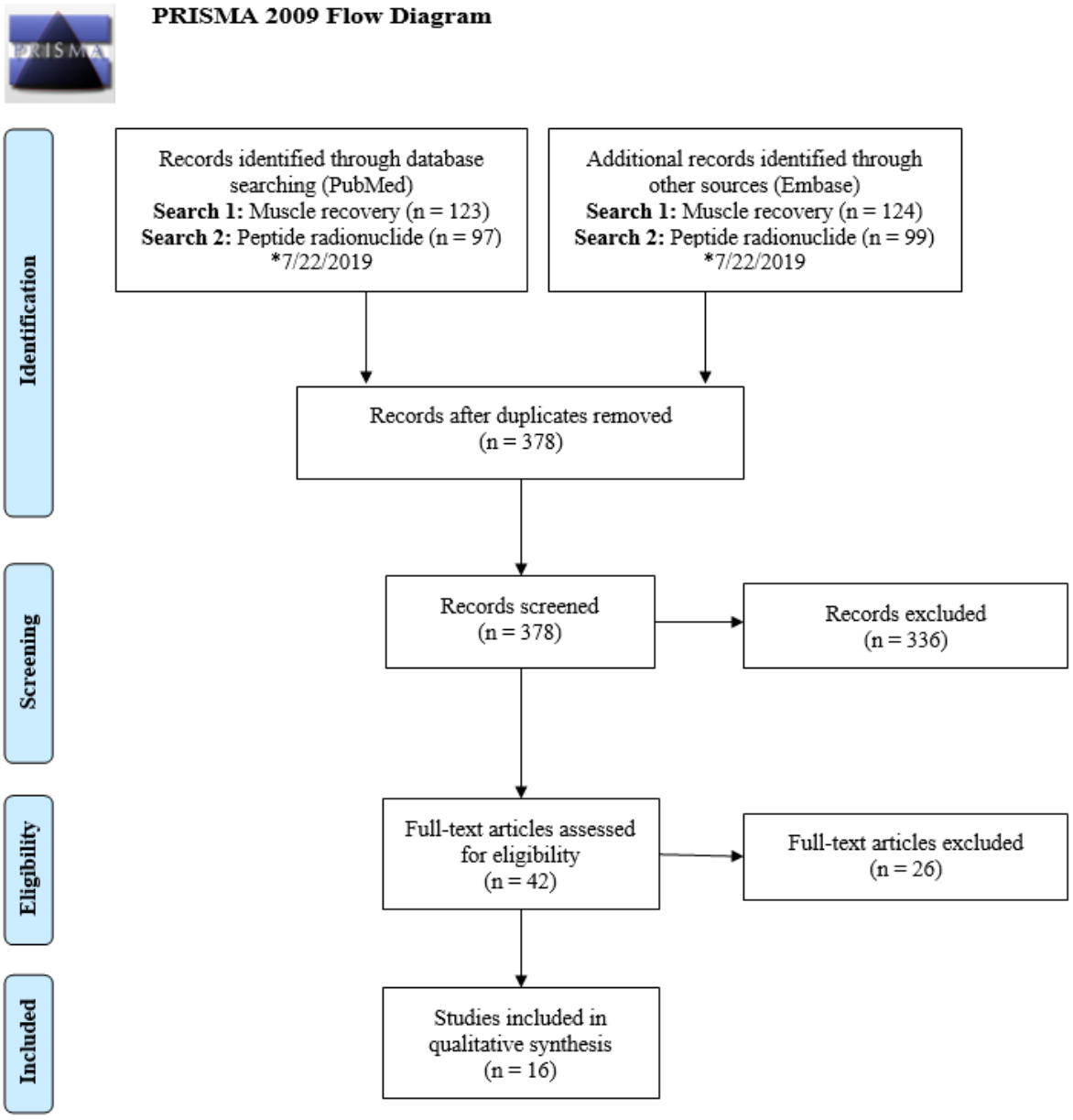
Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram) – Initial Search



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2. Summary of literature screening and selection (PRISMA 2009 Flow Diagram) – Additional Search



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, ten (10) medical specialties that would potentially use lysine HCl were identified: cardiology, endocrinology, hematology, infectious disease, naturopathy, nephrology, neurology, pediatrics, primary care, and psychiatry. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. To determine if a formal interview was warranted, a medical expert in psychiatry was provided the list of substances pertinent to their specialty via email. The expert replied that they do not utilize any of the substances listed. Two (2) experts were contacted for an interview, of which one (1) accepted and one (1) failed to respond to the interview request. The interview was recorded and transcribed via ©Rev.com. QSR International's Nvivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for, endocrinology, hematology, naturopathy, nephrology, neurology, pediatrics, primary care, and psychiatry, identified from the nominations and literature review, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order 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 online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to 13 associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Naturopathy	American Association of Naturopathic Physicians (AANP)
Nephrology	Renal Physicians Association (RPA)
Pediatrics	American Academy of Pediatrics (AAP)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Endocrinology	American Association of Clinical Endocrinologists (AACE)	Declined, "endocrinologists are not generally in the compounding space."
Hematology	American Society of Hematology (ASM)	Failed to respond
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Nephrology	American Society of Nephrology (ASN)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Psychiatry	American Psychiatric Association (APA)	Declined, "we have put this ask to our members and unfortunately, we have not received any information on psychiatrists using compounded products"

CURRENT AND HISTORIC USE

Summary of background information

- Lysine HCl is not available as a single active pharmaceutical ingredient (API) or in combination with L-arginine as an FDA-approved product. However, lysine HCl is available as a multiple API combination injection.
- Lysine HCl is available in various oral dosage forms as an OTC product in the US.
- There is a current United States Pharmacopoeia (USP) monograph for lysine HCl.
- Lysine HCl is available in Abu Dhabi and the EU.

Table 3. Currently approved products – US

No approved products in the US

Table 4. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
L-lysine hydrochloride, L-arginine	25g, 25g	Solution	Infusion	EU	Prescription	07/25/2019
L-lysine	500 mg	Tablets	–	Abu Dhabi	–	–

Abbreviations: "–", not mentioned; ROA, route of administration.

[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.

Summary of literature review

- Total number of studies included: 50 studies (3 descriptive, 45 experimental, and 2 observational).
- Most of the studies were from the US (12).
- Six (6) articles utilized lysine HCl in one of the nominated combination products.
- The most common indications for the use of lysine HCl in the US were herpes simplex and nephroprotection. The most common indications from the non-US studies were nephroprotection, schizophrenia, and lysinuric protein intolerance.
- No compounded products were identified from any US studies. Two (2) non-US studies used a compounded 2.5% solution for nephroprotection.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-3]	3
Experimental[4-48]	45
Observational[49,50]	2

Table 6. Number of studies by country

Country	Number of Studies
Austria[35,38]	2
Chile[8]	1
Denmark[20]	1
Finland[15,16,28]	3
France[27]	1
Germany[21,22,42]	3
India[3,26,40,41,47,48]	6
Iran[33]	1
Italy[6,11,17,23]	4
Japan[25]	1
Pakistan[37]	1
Romania[9]	1

Spain[49]	1
Sweden[30,31,39,43]	4
The Netherlands[36,46]	2
UK[2,44,45,50]	4
US[1,4,7,10,13,14,18,19,24,29,32,34]	12
Multiple Countries • Belgium, the Netherlands, US[5] • Venezuela, US[12]	2
	Total US[a]: 14 Total non-US Countries[a]: 38

[a]Studies 5 and 12 counted in both US and non-US total.

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Lysine HCl / L-arginine – oral capsules[12,25]; intravenous solution[5,21] • Lysine 25g / Arginine 25g – intravenous solution[22, 49]	6
Others found in literature	L-lysine / β-hydroxy-β-methylbutyrate / L-arginine[4]	1
	L-lysine / L-alanine / L-glutamic acid / L-tyrosine[7]	1
	L-lysine / Glycine / L-leucine / L-Proline[23]	1
	L-lysine / Glycine / Hyaluronic acid / L-leucine / L-proline[17]	1
	Lysine / Arginine / Other mixed amino acids (Tryptophan, Isoleucine, Threonine, Phenylalanine, Valine, Leucine, Methionine, Histidine, Serine, Cysteine, Alanine, Proline)[5]	1

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Herpes simplex[13,14,19,24]	0.624-1.5g/day	0.312-0.5g	Capsule, tablet	Oral	4-6 months
	–	–	Cream	Topical	At most 21 days
Nephroprotection[5,34]	–	2.5%	Solution	–	4 times
	50g/day	6.88g/L		Intravenous	Once
Age related protein turnover in the elderly[4]	1.5-2.25g/day	1.5-2.25g	Solution	Oral	1 year
Coronary artery disease[18]	–	–	Powder	Oral	4 months

Iron deficiency anemia[1]	–	–	–	–	3 months
Multiple sclerosis[7]	–	–	Solution	–	32 days
Poorly thriving infants[29]	0.25-0.5g/day	–	Feeding formula	Oral	3 weeks
Oral mucositis[32]	1g/day	–	–	–	–
Osteoporosis[10]	0.4-0.8g/day	–	–	Oral	Once-3 days
Type 2 diabetes mellitus[12]	0.5g/day	–	Capsule	Oral	1 year

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Nephroprotection[5,21,22,35-50]	–	0.025g	–	–	Once
	50g	5%			
	3.5-75g	0.972-5%	Solution	Intravenous	Once
	50g/day	6.88g/L			
Schizophrenia[9,30,31,33]	6g/day	–	–	–	4-8 weeks
	6g/day	1g	Capsule	Oral	8 weeks
		–	Solution		4 weeks
Lysinuric protein intolerance[15,16,28]	3.3mmol/kg	–	Solution	Intravenous	Once
	0.05mmol/kg-1.1mmol/kg	–	–	Oral	3 days
	8-46mg/kg/day				0.5-5 years

Oral mucositis[11,23]	–	–	Spray	Oral, topical	2 weeks
Type 2 diabetes mellitus[12,26]	0.5g/day	–	Capsule	Oral	1 year
	1g/day	0.5g	Tablet		2 months
Alopecia[2]	1.5-2g/day	–	–	–	16-52 weeks
Anxiety[25]	2.64g/day	1.32g	Capsule	Oral	7 days
Fatigue[27]	0.2g/day	0.2g	Tonic	Oral	14 days
Herpes simplex[20]	1g/day	0.5g	Tablet	Oral	12 weeks
Mercurial resistant edema[8]	10-40g/day	5g	Solution	Oral	5-47 days
Metabolic alkalosis[6]	–	–	Solution	Intravenous	Once
Uremia[3]	–	–	–	Intravenous	–
Venous leg ulcer[17]	0.0097g	0.0097g	Powder	Topical	70 days

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 10. Compounded products – US

No compounded products from reported studies

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Nephroprotection[22,49]	• 1 liter of solution contains: 31.25 g lysine HCl, 30.24 arginine HCl, and 953.51 g water for injection. The solution was adjusted to pH 6.3-6.5 with 15% NaOH[22]	Solution	2.5%
	• 25 g lysine HCl and 25 g arginine HCl dissolved in 1000 mL water for injection[49]		

Summary of focus groups/interviews of medical experts and specialty organizations

One (1) interview was conducted. Additionally, a medical expert in psychiatry was provided the list of substances including lysine HCl pertinent to their specialty via email; the expert responded that they do not utilize lysine HCl. A medical expert specializing in neurology was contacted, however the interviewee failed to respond to the interview request.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Lysine HCl	Interview Summary Response
END_03	MD	Endocrinology, Diabetes and Metabolism	Academic medical institution	No	• Does not use this substance

Abbreviation: MD, Doctor of Medicine.

Summary of survey results

Table 13. Characteristics of survey respondents [29 people responded to the survey.[a]]

Board Certification	MD	ND	PharmD	No Response
Anesthesiology	7	0	0	0
Clinical Pharmacology	1	0	0	0
Critical Care Medicine	3	0	0	0
Gastroenterology	1	0	0	0
Fellow of the American Board of Naturopathic Oncology	0	1	0	0
Hospice & Palliative Medicine	1	0	0	0
Naturopathic Doctor	0	6	0	0
Naturopathic Physician	0	5	0	0
Pediatrics	5	0	0	0
Pediatric Anesthesiology	3	0	0	0
No Board Certification	1	2	1	0
No Response	0	0	0	9

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor; PharmD, Doctor of Pharmacy.
[a]Some respondents reported more than one terminal clinical degree or board certification.

Table 14. Types of products used, prescribed, or recommended

Types of Products	Respondents, n (N=4[a,c])
Compounded	1[b]
FDA-approved	1
Over-the-counter	1
Dietary	2
Unsure	0
No response	1

[a]Out of 29 respondents, four (4) reported using, prescribing, or recommending multiple types of lysine HCl product.
[b]One (1) respondent used in combination but did not specify the formulation

Table 15. Compounded use of lysine HCl in practice[a]

Indication[b]	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
"Viral infections as part of an immune support infusion"	100mg	1-3 times a week	–	Intravenous	1-2 hours	–

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]One (1) respondent.
[b]Quotations are direct words from respondents.

Table 16. Indications for which lysine HCl is considered a standard therapy[a]

Indication	Standard Therapy			
	Compounded, n (N=1)	Non-compounded, n (N=2)	Unsure, n (N=0)	No Response, n (N=1)
Herpes Simplex	0	1	0	0
Metabolic disease	0	1	0	0
Mouth sore prevention	0	1	0	0
No response	1	0	0	1

[a]Some respondents reported using more than one type of product.

Table 17. Reasons for using a compounded product instead of any FDA-approved product

No survey respondents provided this information

Table 18. Change in frequency of compounded lysine HCl usage over the past 5 years

	Respondents, n (N=1)
No–use has remained consistent	0
Yes–I use it LESS often now	0
Yes–I use it MORE often now	0
No response	1

Table 19. Do you stock non-patient specific compounded lysine HCl in your practice?

	Respondents, n (N=1)
No	0
Yes	0
No response	1

Table 20. Questions related to stocking non-patient specific compounded lysine HCl

No survey respondents provided this information

CONCLUSION

Lysine hydrochloride (Lysine HCl; UNII code:JNJ23Q2COM) and L-lysine (UNII code: K3Z4F929H6) was nominated for inclusion on the 503B Bulks List by AnazaoHealth Corporation, Empower Pharmacy, and the Outsourcing Facilities Association (OFA). While the exact medical condition in which the compounded product is being requested may not be known, lysine HCl may be used to correct lysine deficiency with or without lysinuric protein intolerance as well as prophylaxis and acute treatment of herpes simplex outbreak. Lysine HCl was also nominated for use in osteoporosis, muscle recovery, prevention of mucositis, and reduction of radiolabeled peptides during peptide receptor radionuclide therapy. Additionally, lysine HCl was nominated for use in combination with L-arginine for use post-LUTATHERA treatment, refer to Table 7 for the nominated formulation. Lysine was nominated for use via a 7-10% topical cream and ointment, 100-500mg oral capsules and solutions, and 25-100mg/mL intravenous or intramuscular solutions for injection.

Lysine HCl is available in in the US in various oral dosage forms as an OTC product, as a multiple API injection, and has a current USP monograph. Lysine HCl is available in Abu Dhabi and the EU.

From the literature review conducted, the most common indications in the US were herpes simplex and nephroprotection. The most common indications from the non-US studies were nephroprotection, schizophrenia, and lysinuric protein intolerance. No compounded products were identified from any US studies. Two (2) non-US studies utilized a 2.5% compounded solution for nephroprotection. Six (6) studies utilized one of the nominated combination products.

Two (2) medical experts denied use of lysine HCl. From the survey responses, four (4) out of 29 respondents used lysine HCl. One (1) respondent reported using compounded lysine HCl in an unspecified combination for viral infections as part of an immune support infusion.

REFERENCES

1. D'Alonzo CA. L-Lysine in nutrition and therapy. *Del Med J.* 1960;32:307-310.
2. Rushton DH. Nutritional factors and hair loss. *Clin Exp Dermatol.* 2002;27(5):400-408.
3. Sen DK. CLINICAL ASSESSMENT OF THE USE OF L-LYSINE HCL IN URAEMIA. *J Indian Med Assoc.* 1964;43:446-447.
4. Baier S, Johannsen D, Abumrad N, Rathmacher JA, Nissen S, Flakoll P. Year-long changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of β-hydroxy-β-methylbutyrate (HMB), L-arginine, and L-lysine. *J Parenter Enter Nutr.* 2009;33(1):71-82.
5. Barone R, Pauwels S, De Camps J, et al. Metabolic effects of amino acid solutions infused for renal protection during therapy with radiolabelled somatostatin analogues. *Nephrol Dial Transplant.* 2004;19(9):2275-2281.
6. Bondoli A, Abballe C, de Cosmo G, Sabato AF, Magalini SI. Lysine hydrochloride for the control of metabolic alkalosis: a clinical report. *Resuscitation.* 1980;8(4):223-231.
7. Bornstein MB, Miller A, Slagle S. A pilot trial of cop 1 in exacerbating-remitting multiple sclerosis. *New Engl J Med.* 1987;317(7):408-414.
8. Brailovsky D, Silva C, Del Campo E, Marusic E. The use of 1-lysine monohydrochloride in the treatment of mercurial resistant edema. *Am J Med Sci.* 1959;238:287-296.
9. Chirita R, Sacuiu I, Burlea A, Chirita V. The role of nitric oxide inhibitors in treatment on symptom severity and cognitive deficits in schizophrenia. *Int J Neuropsychopharmacol.* 2012;15((Chirita R.; Sacuiu I.; Burlea A.; Chirita V.) University of Medicine, Iasi, Romania):113.
10. Civitelli R, Villareal DT, Agnusdei D, Nardi P, Avioli LV, Gennari C. Dietary L-lysine and calcium metabolism in humans. *Nutr Burbank Los Angel Cty Calif.* 1992;8(6):400-405.
11. Colella G, Cannavale R, Vicidomini A, Rinaldi G, Compilato D, Campisi G. Efficacy of a spray compound containing a pool of collagen precursor synthetic aminoacids (L-proline, L-leucine, L-lysine and glycine) combined with sodium hyaluronate to manage chemo/radiotherapy-induced oral mucositis: Preliminary data of an open clinical trial. *Int J Immunopathol Pharmacol.* 2010;23(1):143-151.
12. Contreras I, Reiser KM, Martinez N, et al. Effects of aspirin or basic amino acids on collagen cross-links and complications in NIDDM. *Diabetes Care.* 1997;20(5):832-835.
13. DiGiovanna JJ, Blank H. Failure of lysine in frequently recurrent herpes simplex infection. Treatment and prophylaxis. *Arch Dermatol.* 1984;120(1):48-51.
14. Griffith RS, Walsh DE, Myrmel KH. Success of L-lysine therapy in frequently recurrent herpes simplex infection. Treatment and prophylaxis. *Dermatologica.* 1987;175(4):183-190.
15. Lukkarinen M, Näntö-Salonen K, Pulkki K, Aalto M, Simell O. Oral supplementation corrects plasma lysine concentrations in lysinuric protein intolerance. *Metabolism.* 2003;52(7):935-938.
16. Lukkarinen M, Nanto-Salonen K, Pulkki K, Mattila K, Simell O. Effect of lysine infusion on urea cycle in lysinuric protein intolerance. *Metabolism.* 2000;49(5):621-625.

17. Maggio G, Armenio A, Ruccia F, Giglietto D, Pascone M, Ribatti D. A new protocol for the treatment of the chronic venous ulcers of the lower limb. *Clin Exp Med.* 2012;12(1):55-60.

18. Maniscalco BS, Taylor KA. Calcification in coronary artery disease can be reversed by EDTA-tetracycline long-term chemotherapy. *Pathophysiology.* 2004;11(2):95-101.

19. McCune MA, Perry HO, Muller SA, O'Fallon WM. Treatment of recurrent herpes simplex infections with L-lysine monohydrochloride. *Cutis.* 1984;34(4):366-373.

20. Milman N, Scheibel J, Jessen O. Lysine prophylaxis in recurrent herpes simplex labialis: a double-blind, controlled crossover study. *Acta Derm Venereol.* 1980;60(1):85-87.

21. Pfob CH, Ott A, Maurer F, et al. Hyperkalemia in patients treated with radioligand or peptide receptor radionuclide therapy. *Eur J Nucl Med Mol Imag.* 2017;44(2):S327.

22. Pfob CH, Eiber M, Luppa P, et al. Hyperkalemia in patients treated with endoradiotherapy combined with amino acid infusion is associated with severe metabolic acidosis. *EJNMMI Research.* 2018;8.

23. Ruggiero T, Pol R, Camisassa D, Simiele S, Giaccone L, Carossa S. Treatment of symptomatic oral mucositis with sodium hyaluronate and synthetic amino acid precursors of collagen in patients undergoing haematopoietic stem cell transplantation. *J Biol Regul Homeost Agents.* 2018;32(3):737-743.

24. Singh BB, Udani J, Vinjamury SP, et al. Safety and effectiveness of an L-lysine, zinc, and herbal-based product on the treatment of facial and circumoral herpes. *Altern Med Rev.* 2005;10(2):123-127.

25. Smriga M, Ando T, Akutsu M, Furukawa Y, Miwa K, Morinaga Y. Oral treatment with L-lysine and L-arginine reduces anxiety and basal cortisol levels in healthy humans. *Biomedical Research.* 2007;28(2):85-90.

26. Sulochana KN, Rajesh M, Ramakrishnan S. Insulin receptor tyrosine kinase activity in monocytes of type 2 diabetes mellitus patients receiving oral L-lysine. *Indian J Biochem Biophys.* 2001;38(5):331-334.

27. Taieb C, Rahalli N, Auges M. Fatigue management: Example in pharmacies. *Pharmacoepidemiol Drug Saf.* 2011;20((Taieb C.; Rahalli N.; Auges M.) Public Health, PFSA, Paris, France):S41-S42.

28. Tanner LM, Näntö-Salonen K, Niinikoski H, Huoponen K, Simell O. Long-term oral lysine supplementation in lysinuric protein intolerance. *Metabolism.* 2007;56(2):185-189.

29. Vignec AJ, Gasparik MZ. Effect of dietary supplementation with L-lysine in poorly thriving infants. *N Y State J Med.* 1959;59(10):1998-2002.

30. Wass C, Klamer D, Katsarogiannis E, et al. L-lysine as adjunctive treatment in patients with schizophrenia: A single-blinded, randomized, cross-over pilot study. *BMC Med.* 2011;9.

31. Wass CE. The nitric oxide signalling system as a potential treatment target for information processing deficits in schizophrenia. *Biol Psychiatry.* 2012;71(8):124S.

32. Wong WM, Liao JJ, Laramore GE, Valley JJ, Polissar NL, Parvathaneni U. L-lysine in the treatment of oral mucositis in head-and-neck cancer patients: A pilot study. *Int J Radiat Oncol Biol Phys.* 2013;87(2):S568.

33. Zeinoddini A, Ahadi M, Farokhnia M, Rezaei F, Tabrizi M, Akhondzadeh S. L-lysine as an adjunct to risperidone in patients with chronic schizophrenia: A double-blind, placebo-controlled, randomized trial. *J Psychiatr Res.* 2014;59:125-131.

34. Bodei L, Cremonesi M, Ferrari M, et al. Renal protection during lutathera treatment using lysine and arginine solutions. *Eur J Nucl Med Mol Imag.* 2018;45:S288-S289.

35. Duan H, Dolliner P, Dobrozemsky G, Raderer M, Hoffmann M. Peptide receptor radionuclide therapy proves to be safe and immediately efficient in elderly patients with symptomatic neuroendocrine tumours. *Eur J Nucl Med Mol Imag.* 2013;40:S199-S200.

36. Esser JP, Krenning EP, Teunissen JJM, et al. Comparison of [177Lu-DOTA0,Tyr3]octreotate and [177Lu-DOTA0,Tyr3]octreotide: Which peptide is preferable for PRRT? *Eur J Nucl Med Mol Imag.* 2006;33(11):1346-1351.

37. Fatima A, Zaidi SSA. Analysing the effectiveness peptide receptor radionuclide therapy with 177Lu-DOTATATE. A journey towards optimising the treatment options for NET. *Neuroendocrinology.* 2019;108:210.

38. Gabriel M, Andergassen U, Putzer D, et al. Individualized peptide-related-radionuclide-therapy concept using different radiolabelled somatostatin analogs in advanced cancer patients. *Q J Nucl Med Mol Imaging.* 2010;54(1):92-99.

39. Garkavij M, Samarzija M, Ewers SB, Jakopovic M, Tezak S, Tennvall J. Concurrent radiotherapy and tumor targeting with 111In-HMFG1-F(ab')2 in patients with MUC1-positive non-small cell lung cancer. *Anticancer Res.* 2005;25(6c):4663-4671.

40. Gupta SK, Singla S, Bal C, Bal C. Dosimetric studies of 177Lu-DOTATATE Administered into Neuroendocrie Tumors. *Eur J Nucl Med Mol Imag.* 2012;39:S295.

41. Gupta SK, Singla S, Thakral P, Bal CS. Dosimetric analyses of kidneys, liver, spleen, pituitary gland, and neuroendocrine tumors of patients treated with 177Lu-DOTATATE. *Clin Nucl Med.* 2013;38(3):188-194.

42. Lapa C, Werner RA, Bluemel C, et al. Influence of the amount of co-infused amino acids on post-therapeutic potassium levels in peptide receptor radionuclide therapy. *EJNMMI Res.* 2014;4:46.

43. Larsson M, Bernhardt P, Svensson JB, Wangberg B, Ahlman H, Forssell-Aronsson E. Estimation of absorbed dose to the kidneys in patients after treatment with 177Lu-octreotate: comparison between methods based on planar scintigraphy. *EJNMMI Res.* 2012;2(1):49.

44. Maclean J, Haroon A, Walker C, et al. 177Lu-DOTA therapy for recurrent meningioma: A pilot study. *Eur J Nucl Med Mol Imag.* 2012;39:S333.

45. Maclean J, Walker C, Gaze M, et al. Targeted radionuclide therapy for metastatic pituitary carcinoma. *Radiother Oncol.* 2012;102:S132-S133.

46. Rolleman EJ, Valkema R, de Jong M, Kooij PP, Krenning EP. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. *Eur J Nucl Med Mol Imaging.* 2003;30(1):9-15.

47. Yadav M, Ballal S, Tripathi M, et al. Post-therapeutic dosimetry of 177Lu-DKFZ-PSMA-617 in treatment of patients with castration resistant prostate cancer. *J Nucl Med.* 2016;57.

48. Yadav MP, Ballal S, Tripathi M, et al. Post-therapeutic dosimetry of 177Lu-DKFZ-PSMA-617 in the treatment of patients with metastatic castration-resistant prostate cancer. *Nucl Med Commun.* 2017;38(1):91-98.

49. Sáez-Garrido M, Juan José FA, Agustina RG, et al. Making of an amino-acid solution for nephrotoxicity prevention in patients treated with lutetium-octreotate 177 radioactive isotope. *Eur J Hosp Pharm.* 2018;25:A26.

50. Davis LM, Martin W, Nicou N, et al. PRRT improved survival in patients with neuroendocrine neoplasm and carcinoid heart disease treated surgically in a centre of excellence. *Nucl Med Commun.* 2018;39(4):375.

APPENDICES

Appendix 1. Search strategies for new nominations

PubMed search strategy 1: muscle recovery

- Years searched: 1946 to present
- Limits: English language
- Date searched: July 22, 2019
- Number of results: 123

1	Search "lysine"[MeSH] OR lysin*[tiab]	88280
2	Search "muscle, skeletal"[MeSH] OR "muscle strength"[MeSH] OR "muscle fatigue"[MeSH] OR "recovery of function"[MeSH] OR "skeletal muscle"[tiab] OR "skeletal muscles"[tiab] OR "skeletal musculature"[tiab] OR "muscle recovery"[tiab] OR "muscular recovery"[tiab] OR "muscle fatigue"[tiab] OR "muscular fatigue"[tiab]	381549
3	Search "drug combinations"[MeSH] OR "drug compounding"[MeSH] OR "therapeutic use"[subheading] OR "drug therapy"[subheading] OR "administration and dosage"[subheading] OR "drug effects"[subheading] OR treat*[tiab] OR therap*[tiab] OR compound*[tiab]	10534816
4	Search ("animals"[MeSH] NOT "humans"[MeSH])	4600537
5	Search (#1 AND #2 AND #3)	444
6	Search (#5 NOT #4) AND english[lang]	123

PubMed search strategy 2: peptide receptor radionuclide therapy

- Years searched: 1946 to present
- Limits: English language
- Date searched: July 22, 2019
- Number of results: 97

1	Search ("lysine"[MeSH] OR lysin*[tiab])	91605
2	Search ("radiopharmaceuticals"[MeSH] OR "radioisotopes"[MeSH:noexp] OR "lutetium"[MeSH] OR "octreotide"[MeSH] OR "peptide receptor radionuclide therapy"[tiab] OR "peptide related radionuclide therapy"[tiab] OR "peptide radionuclide therapy"[tiab] OR "octreotate"[tiab] OR "octreotide"[tiab] OR "lutetium"[tiab] OR "lutathera"[tiab])	10534816
3	Search (("drug combinations"[MeSH] OR "drug compounding"[MeSH] OR "therapeutic use"[subheading] OR "drug therapy"[subheading] OR "administration and dosage"[subheading] OR "drug effects"[subheading] OR treat*[tiab] OR therap*[tiab] OR compound*[tiab])	4600537
4	Search ("animals"[MeSH] NOT "humans"[MeSH])	161

5	Search (#1 AND #2 AND #3)	99
6	Search (#5 NOT #4)	97

Embase search strategy 1: muscle recovery

- Platform: Elsevier
- Years searched: 1947 to present
- Limits: English language
- Date searched: July 22, 2019
- Number of results: 124

1	lysine'/de	57588
2	lysin$':ti,ab	82915
3	#1 OR #2	104999
4	skeletal muscle'/exp	361433
5	muscle strength'/de	67194
6	muscle fatigue'/de	12397
7	(muscl* NEAR/2 (fatigue$ OR recover$)):ti,ab	9759
8	skeletal muscl*':ti,ab	137178
9	#4 OR #5 OR #6 OR #7 OR #8	458550
10	drug combination'/de	120101
11	drug formulation'/de	115479
12	drug therapy':lnk	3730827
13	drug combination':lnk	804980
14	drug comparison':lnk	582238
15	drug administration':lnk	1667508
16	treat*':ti,ab	7431367
17	therap*':ti,ab	3880054
18	compound*':ti,ab	975613
19	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	11903936

20	[animals]/lim NOT [humans]/lim	5868146
21	#3 AND #9 AND #19	352
22	#21 NOT #20	134
23	#21 NOT #20 AND [english]/lim	124

Embase search strategy 2: peptide receptor radionuclide therapy

- Platform: Elsevier
- Years searched: 1947 to present
- Limits: English language
- Date searched: July 22, 2019
- Number of results: 99

1	lysine'/de	57588
2	lysin$':ti,ab,tn	82923
3	#1 OR #2	104999
4	lutetium chloride lu 177'/de	10
5	lutetium 177'/de	3319
6	octreotide'/de OR 'oxodotreotide lu 177'/de	21566
7	(peptide NEAR/2 radionuclide):ti,ab	1524
8	lutetium':ti,ab OR 'lutathera':ti,ab OR 'octreot*':ti,ab OR 'oxodotreotide':ti,ab	12989
9	#4 OR #5 OR #6 OR #7 OR #8	424414
10	drug combination'/de	120296
11	drug formulation'/de	115556
12	drug therapy':lnk	3732311
13	drug combination':lnk	805256
14	drug comparison':lnk	582450
15	drug administration':lnk	1668194
16	treat*':ti,ab	7433017
17	therap*':ti,ab	3882414

18	compound*':ti,ab	975613
19	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	11903936
20	[animals]/lim NOT [humans]/lim	5868146
21	#3 AND #9 AND #19	151
22	#21 NOT #20	102
23	#21 NOT #20 AND [english]/lim	99

Appendix 2. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **lysine HCl**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. 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. If you have additional questions or concerns about this research 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.

End of Block: Welcome Page

Start of Block: Lysine HCl

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **lysine HCl**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☐ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ☐ Unsure

Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for lysine HCl? Please check all th... != Compounded drug product

Skip To: Q2 If What type(s) of product(s) do you use, prescribe, or recommend for lysine HCl? Please check all th... = Compounded drug product

---

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for lysine HCl? Please check all th... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **lysine HCl** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **lysine HCl** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q5 If Do you use compounded lysine HCl as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded lysine HCl as a single agent active ingredient, or as one active ingredient... = Combination

Q4. Please list all combination products in which you use compounded **lysine HCl**.

_____

Q5. For which, if any, diseases or conditions do you consider compounded **lysine HCl** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **lysine HCl** in medical practice guidelines or other resources?

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **lysine HCl** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why) _____
- ○ Yes - I use it **LESS** often now (briefly describe why) _____
- ○ No - use has remained consistent

Q8. Why do you use compounded **lysine HCl** instead of any FDA-approved drug product?

_____

Q9. Do you stock non-patient-specific compounded **lysine HCl** in your practice location?

- o Yes
- o No

Skip To: End of Block If Do you stock non-patient-specific compounded lysine HCl in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded lysine HCl in your practice location? = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **lysine HCl**? Please check all that apply.

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **lysine HCl**? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **lysine HCl**? Please check all that apply.

- ☐ Convenience
- ☐ Emergencies
- ☐ Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded lysine HCl? Please check all that apply. = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded lysine HCl? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded lysine HCl? Please check all that apply. = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **lysine HCl** standard therapy?

_____

Q14. Does your specialty describe the use of **lysine HCl** in medical practice guidelines or other resources?

_____

End of Block: Lysine HCl

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ☐ Doctor of Medicine (MD)
- ☐ Doctor of Osteopathic Medicine (DO)
- ☐ Doctor of Medicine in Dentistry (DMD/DDS)
- ☐ Naturopathic Doctor (ND)
- ☐ Nurse Practitioner (NP)
- ☐ Physician Assistant (PA)
- ☐ Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ☐ No Board certification
- ☐ Allergy and Immunology
- ☐ Anesthesiology
- ☐ Cardiovascular Disease
- ☐ Critical Care Medicine
- ☐ Dermatology
- ☐ Emergency Medicine
- ☐ Endocrinology, Diabetes and Metabolism
- ☐ Family Medicine
- ☐ Gastroenterology
- ☐ Hematology
- ☐ Infectious Disease
- ☐ Internal Medicine
- ☐ Medical Toxicology
- ☐ Naturopathic Doctor
- ☐ Naturopathic Physician
- ☐ Nephrology
- ☐ Neurology
- ☐ Obstetrics and Gynecology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Otolaryngology
- ☐ Pain Medicine
- ☐ Pediatrics
- ☐ Psychiatry
- ☐ Rheumatology
- ☐ Sleep Medicine
- ☐ Surgery (please describe) _____
- ☐ Urology
- ☐ Other (please describe) _____

End of Block: Background Information