Summary Report

Lansoprazole

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
PPI	Proton pump inhibitor
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 lansoprazole (UNII code: 0K5C5T2QPG), 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 lansoprazole 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 lansoprazole 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 lansoprazole 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

Lansoprazole was nominated for inclusion on the 503B Bulks List by Fagron.

Lansoprazole was nominated for short-term treatment of erosive esophagitis for up to 7 days via a 6 mg/mL injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of lansoprazole.[6-8]

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

- The FDA-approved omeprazole injection contains PEG-400 which can cause allergic reactions (note: omeprazole is not currently and has never been available as an FDA-approved injection product)
- The FDA-approved lansoprazole injection has been discontinued
- FDA-approved drug products that contain lansoprazole are either capsules or tablets, which are unsuitable for compounding an injection

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of lansoprazole 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 lansoprazole; name variations of lansoprazole 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 lansoprazole. 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

Lansoprazole is a component of an FDA-approved product that was discontinued by the manufacturer, not for safety or efficacy reasons. The nominated compounded products did not differ substantially from the commercially available product. Therefore, a systematic literature review was not conducted.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances lansoprazole was used in a clinical setting. The systematic literature review and indication from the nomination was reviewed to identify the following medical specialties that would potentially use lansoprazole: gastroenterology and otolaryngology. 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 lansoprazole 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

- Lansoprazole is not available as an FDA-approved product in the nominated dosage form and ROA.
- Lansoprazole was available as an FDA-approved injectable product that was discontinued, not for reasons of safety or efficacy.
- Lansoprazole is not available as an OTC product in the nominated dosage form and ROA in the US.
- There is a current United States Pharmacopeia (USP) monograph for lansoprazole.
- Lansoprazole is not available in the nominated dosage form and ROA in any of the national medical registers 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

No literature review was conducted.

Pharmacology and historical use

Two studies were identified that provided valuable information about the pharmacology and historical use of lansoprazole.

While several of the proton pump inhibitors (PPIs) are available via the oral route, and some of them as OTC products, there are still advantages to intravenous administration. Intravenous lansoprazole provides a greater intragastric pH within the first hour after administration when compared to oral preparations.[9]

In a 2006 review, the authors mentioned three PPIs (esomeprazole, lansoprazole, pantoprazole) that had an injectable dosage form; of these 3, only lansoprazole was FDA-approved for "short-term treatment (up to 7 [days]) of all grades of erosive esophagitis in patients unable to take oral therapy."[9] The other 2 were approved for "short-term treatment (up to 10 [days]) of gastroesophageal reflux disease associated with a history of erosive esophagitis in patients for whom oral therapy is not possible or appropriate."[9]

In a prospective randomized study comparing esomeprazole 40 mg once daily to lansoprazole 30 mg once daily (the ROA was not specified), the authors determined that "esomeprazole was significantly

more effective than lansoprazole with regard to total and supine nocturnal percentage acid reflux time."[10]

Table 3. Types of studies

No literature review was conducted

Table 4. Number of studies by country

No literature review was conducted

Table 5. Summary of included studies

No literature review was conducted

Table 6. Dosage by indication – US

No literature review was conducted

Table 7. Dosage by indication – non-US countries

No literature review was conducted

Table 8. Number of studies by combination

No literature review was conducted

Table 9. Compounded products – US

No literature review was conducted

Table 10. Compounded products – non-US countries

No literature review was conducted

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. Two SMEs discussed lansoprazole. Amongst these 2 SMEs, there was 1 medical doctor and 1 physician assistant. The SMEs specialized and/or were board-certified in gastroenterology and hepatology, working in academic medical centers and private practice/clinics. The SMEs had been in practice for 9 to 50 years.

Patients who would need an intravenous PPI would be those with a gastrointestinal bleed, unable to take anything by mouth, significant dysphagia or odynophagia, or at risk of aspiration. There are other PPIs that are currently available as injectable products, including pantoprazole and esomeprazole. The SMEs were not familiar with PEG-400 causing allergic reactions in patients. There may be other side effects, such as urticaria or significant tachyphylaxis, but this has not been a barrier for inpatient treatment. Injectable PPIs are not used in the outpatient setting; one SME stated that they have enough trouble getting patients to do a B-12 injection, much less a PPI injection once or twice daily.

One SME said that intravenous lansoprazole was probably discontinued because it was not profitable for the manufacturer.

Results of survey

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

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which lansoprazole prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded lansoprazole

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

CONCLUSION

Lansoprazole was nominated for inclusion on the 503B Bulks List via an injection for the short-term treatment of erosive esophagitis. Lansoprazole is not available in the nominated dosage form and ROA in any of the national medical registries searched. It was previously available as an FDA-approved injectable product but was discontinued by the manufacturer for reasons unrelated to safety or efficacy.

From the literature review and interviews, injectable lansoprazole was the only injectable PPI that was FDA-approved specifically for erosive esophagitis; esomeprazole and pantoprazole are FDA-approved for short-term treatment of gastroesophageal reflux disease associated with a history of erosive esophagitis. There was no information supporting the use of lansoprazole over the other therapies; a study comparing esomeprazole and lansoprazole (unspecified ROA) found esomeprazole to be more effective than lansoprazole. While one of the reasons the nominator suggested lansoprazole for the 503B Bulks List was allergic reactions associated with injectable FDA-approved omeprazole, omeprazole is not currently and has never been available as an FDA-approved injection product. The SMEs were not familiar with any allergic reactions or side effects with the available injectable PPIs that would prevent them from using them in patients requiring intravenous PPI therapy.

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

No literature review was conducted.

Appendix 2. Survey instrument

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

   - o Yes
   - o No

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

   - o Solution for injection
   - o None of the above

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

   - o Erosive esophagitis
   - o Other (please explain) _____

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

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

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

7. I obtain compounded lansoprazole 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.