Summary Report

Ipamorelin acetate

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Prepared by:

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Table of Contents

INTRODUCTION 5
REVIEW OF NOMINATION 5
METHODOLOGY 5
Background information 5
Systematic literature review 6
Interviews 7
Survey 7
CURRENT AND HISTORIC USE 8
Results of background information 8
Results of literature review 8
Results of interviews 13
Results of survey 14
CONCLUSION 18
REFERENCES 19
APPENDICES 20
Appendix 1. Search strategies for bibliographic databases 20
Appendix 2.1. Survey instrument for professional medical associations 22
Appendix 2.2. Survey instrument for Ambulatory Surgery Center Association 25
Appendix 3. Survey distribution to professional associations 28

Table of Tables

Table 1. Currently approved products – US 8
Table 2. Currently approved products – select non-US countries and regions 8
Table 3. Types of studies 11
Table 4. Number of studies by country 11
Table 5. Summary of included studies 12
Table 6. Dosage by indication – US 12
Table 7. Dosage by indication – non-US countries 12
Table 8. Number of studies by combination 12
Table 9. Compounded products – US 12
Table 10. Compounded products – non-US countries 13
Table 11. Characteristics of survey respondents 14
Table 12. Conditions for which ipamorelin acetate prescribed or administered 14
Table 13. Reasons for using compounded ipamorelin acetate 14
Table 14. Use of non-patient-specific compounded ipamorelin acetate 14
Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms 15
Table 16. Products obtained from a 503B outsourcing facility 15
Table 17. Type of specialty procedures performed at ambulatory surgery facility 17

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 ipamorelin acetate (UNII code: Y9M3S78FZ6), 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 ipamorelin acetate 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 ipamorelin acetate 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 ipamorelin acetate 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

Ipamorelin acetate was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA).

Ipamorelin acetate was nominated for postoperative ileus via a 0.5-5 mg/mL injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology, and support the clinical use, of ipamorelin acetate.[6,7]

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

- There are no FDA-approved products that contain ipamorelin acetate.
- The compounded product may be the only thing to effectively treat the indication.
- A patient may need a prescribed dosage form or strength not available commercially.
- Possible patient sensitivities or allergies to inactive ingredients.
- Manufacturer backorders.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of ipamorelin acetate 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 ipamorelin acetate; name variations of ipamorelin acetate 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 ipamorelin acetate. 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 ipamorelin acetate (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. No limits were applied to the searches. Searches were conducted on November 30, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 7, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on November 7, 2019 for clinical practice guidelines that recommended the use of ipamorelin acetate and provided sufficient dosing and administration instructions.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which ipamorelin acetate 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 ipamorelin acetate 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 ipamorelin acetate 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 ipamorelin acetate; setting;

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

- Ipamorelin acetate is not available as an FDA-approved product in the nominated dosage form and ROA.
- Ipamorelin acetate is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for ipamorelin acetate.
- Ipamorelin acetate is not available in any of the national medical registries searched in the nominated form and ROA.

Table 1. Currently approved products – US

No approved products in the US

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

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 133 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 96 titles and abstracts were screened. After screening, the full text of 3 articles was reviewed. Finally, 1 study was included. Two studies were excluded for the following reasons: wrong study design (1 study); ipamorelin acetate not used clinically (1).

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

Characteristics of included studies

The 1 included experimental study was published in the US in 2014.

A total of 117 patients participated in the included study.

Outcome measure was tolerance of standardized solid meal.

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

Use of ipamorelin acetate

Fifty-six patients received ipamorelin acetate as an experimental treatment for postoperative ileus, administered intravenously in 0.03 mg/kg doses. Duration of treatment ranged from 7 days or until hospital discharge, whichever occurred first.

Refer to Table 6 for summaries of dosage by indication.

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

In the included study, the authors concluded that further studies were necessary on the treatment of postoperative ileus with ipamorelin acetate.[6] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

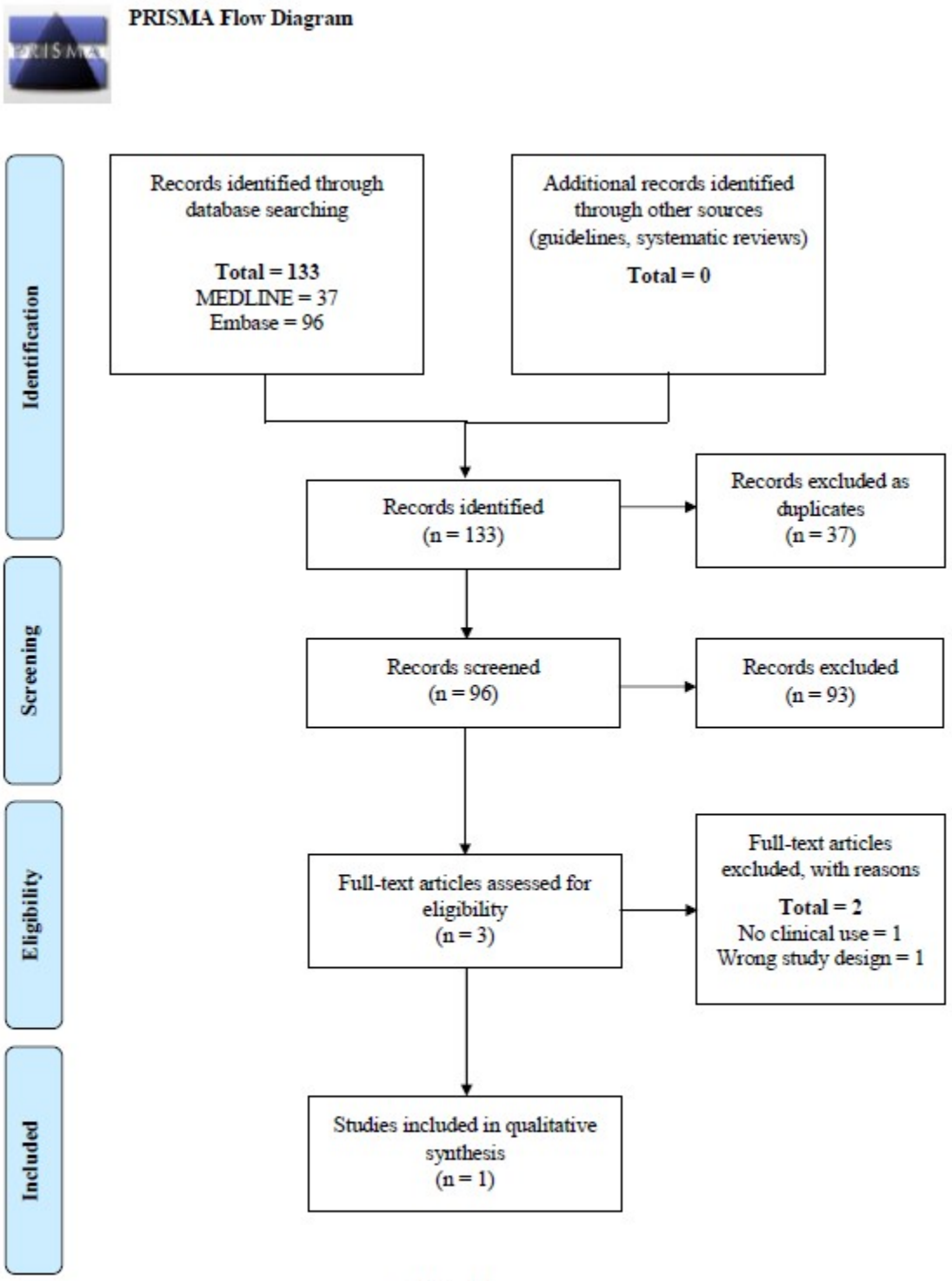
In addition to the 1 included study, 3 articles were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of ipamorelin acetate.

Postoperative ileus is a temporary impairment of gastrointestinal motility, and typically occurs as a consequence of abdominal surgeries.[8,9] While this usually resolves quickly, prolonged and untreated incidents of postoperative ileus may lead to patients requiring nasogastric intubation or parenteral nutrition.[9] While the cause of postoperative ileus is unknown, the main factors are delayed gastric emptying and intestinal transit.[9] Opioids have also been known to exacerbate the symptoms of postoperative ileus.[8,9]

In a 2017 review by Stakenborg, the author lists 3 potential pharmacological strategies to treat postoperative ileus: prokinetics, opioid antagonists, and ghrelin agonists.[8] The two ghrelin agonists evaluated in this review (ipamorelin and ulimorelin) were not shown to improve management of postoperative ileus, therefore "dampening the enthusiasm to develop this class of compounds as treatment for [postoperative ileus]."[8]

The authors of the included study conducted a Phase 2 dose-finding study with ipamorelin acetate in patients with small and/or large bowel resection to explore various dose levels and frequencies at 0.06-0.18 mg/kg/day (ClinicalTrials.gov identifier NCT01280344).[10] No results were posted at the time of this review.[10]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive	0
Observational	0
Experimental[6]	1

Table 4. Number of studies by country

Country	**Number of Studies**
US[6]	1
	Total US: 1 Total Non-US Countries: 0

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Postoperative ileus					
Beck *et al.*, 2014, US[6]	Double-blind placebo-controlled clinical trial	117 In-patients after small or large bowel resection via open or laparoscopic surgery (54%, range 21-84 y)	• Ipamorelin acetate (56) • Placebo (61)	Tolerance of standardized solid meal	Ipamorelin was well tolerated, but there was no significant difference between ipamorelin and placebo

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Postoperative ileus after bowel resection[6]	0.06 mg/kg/day	–	–	Intravenous	Until hospital discharge, up to 7 days

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No 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. Eight SMEs discussed ipamorelin acetate. Amongst these 8 SMEs, there were 5 medical doctors, 1 nurse practitioner, 1 physician assistant, and 1 regulatory affairs specialist. The SMEs specialized and/or were board-certified in gastroenterology, hepatology, intestinal diseases, oncology/hematology, palliative care, sexual/reproductive health, and urology, working in academic medical center, pharmacy/pharmaceutical company, and private practice/clinic. The SMEs had been in practice for 9 to 50 years.

The occurrence of postoperative ileus is common in abdominal surgeries. One SME said that you can see an underlying gastrointestinal dysmotility in preoperative histories and when combined with anesthesia, surgical intervention, and new medications, ileus can occur. The management of postoperative ileus depends on the initial cause of the impairment. If linked to opioid use, then SMEs use bowel regimen medications, Relistor® (methylnaltrexone) or Entereg® (alvimopan). If they think the patient is at risk for Ogilvie's syndrome (an acute colonic pseudo-obstruction), then they might use neostigmine. However, it is not always known what caused the ileus; typically, it resolves with time. The SME knows that the postoperative ileus has resolved when bowel function has returned, patients no longer feel bloated, and can keep oral contents down. At this point, the colonic rectal decompression and nasogastric (NG) tubes are removed. One SME recalled a situation where a patient who presented with a sigmoid volvulus (a torsion of an alimentary tract segment) required a partial colectomy. The patient exhibited significant bowel dysmotility, struggled postoperatively, and required a decompression tube and parenteral nutrition. With time, the bowel dysmotility resolved. In general, the SMEs said that they were not familiar with the use of ipamorelin acetate for postoperative ileus in any patient population. Several SMEs said that they could see a use for ipamorelin acetate, but their practice does not involve procedures that put the patient at risk of postoperative ileus.

Several urologist SMEs discussed ipamorelin acetate being used for patients with growth hormone deficiencies. In addition to ipamorelin acetate being a ghrelin agonist, it is also a somatostatin inhibitor, which is a downstream inhibitor of the growth hormone pathway. One SME said that there is a "trending" synergistic combination of ipamorelin acetate with CJC-1295, which essentially acts as a growth hormone-releasing hormone (GHRH). When administered together, the SME said that "you're stepping on the gas and you're releasing the brake, so that's where the synergy comes from." This combination is administered via once daily injection, at night when the growth hormone pathway is most active. Practitioners track insulin-like growth factor-1 (IGF-1) levels and will adjust the dose based off these levels. However, it takes a while for IGF-1 to increase as a result of the injections, and there is a point where the body will no longer respond to increased doses. As a result, "it's very hard to overshoot" patients on growth hormone. Another SME said that while they have not used ipamorelin acetate before, they "can see its benefit being very similar to IGF-1 boosting agents" and therefore, they thought it makes sense to allow those to continue.

Ipamorelin acetate was previously compounded in a 503B facility, but one SME said that it is no longer produced due to changes based on regulations and updates.

Results of survey

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

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.2 for survey instrument).

Amongst respondents to the ASCA survey, 97 (42% of 230 total respondents) were very familiar with the term '503B outsourcing facility,' 86 (37%) were somewhat familiar with this term, and 47 (20%) were not familiar with this term (refer to Table 15).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. One respondent (0.34% of 290 responses, where respondents were allowed to select multiple drug products) obtained ipamorelin acetate from a 503B outsourcing facility (refer to Table 16).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 17).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which ipamorelin acetate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded ipamorelin acetate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded ipamorelin acetate

No respondents to survey distributed via professional medical associations

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	**Responses, n (N=230)**
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	**Responses, n (N=290)[a]**
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3
Fentanyl	10

Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanil	4
Sufentanil	2
Tramadol	2
None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

[a]Survey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	Responses, n (N=686)[a]
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other[b]	40

[a]Survey respondents were allowed to select multiple procedure types.
[b]No respondents provided description for 'Other' procedure type.

CONCLUSION

Ipamorelin acetate was nominated for inclusion on the 503B Bulks List as an injection to treat postoperative ileus. Ipamorelin acetate is not available in the nominated dosage form and ROA in any of the national medical registries searched.

From the literature review and interviews, postoperative ileus is a temporary impairment of gastrointestinal motility that occurs as a result of abdominal surgeries. The cause is largely unknown, though symptoms are due to delayed gastric emptying and intestinal transit and may be exacerbated by opioid use. Pharmacological strategies used to treat postoperative ileus include prokinetics, opioid antagonists (such as alvimopan and methylnaltrexone), and ghrelin agonists. Ghrelin agonists that have been evaluated for postoperative ileus have not been shown to improve postoperative ileus management. In general, the postoperative ileus resolves with time, and is known to be resolved when the patient has return of their bowel function, no longer feels bloated, and can keep oral contents down. The SMEs were not familiar with the use of ipamorelin acetate for postoperative ileus, but several said that they could see the potential, despite not practicing surgeries that are at risk for ileus. In addition, several SMEs mentioned using ipamorelin acetate in combination with CJC-1295 for patients with growth hormone deficiency. Ipamorelin acetate was previously compounded in a 503B facility, but they have stopped producing it due to changes in regulations.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Two hundred thirty people responded to the survey distributed via the ASCA. One respondent reported obtaining ipamorelin from a 503B outsourcing facility.

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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 November 27, 2019
- Date last searched: November 30, 2019
- Limits: None
- Number of results: 37
- Notes: Included investigational drug numbers because few results

1	ipamorelin$.tw.	37
2	("nnc 26 0161" or "nnc26 0161" or nnc 260161).tw.	1
3	or/1-2	37

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: November 30, 2019
- Limits: None
- Number of results: 96
- Notes: Included investigational drug numbers because few results

1	ipamorelin'/de	89
2	ipamorelin':ti,ab,tn	52
3	nnc 26 0161':ti,ab,tn OR 'nnc26 0161':ti,ab,tn OR 'nnc 260161':ti,ab,tn	7
4	#1 OR #2 OR #3	96

Appendix 2.1. Survey instrument for professional medical associations

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

   - o Yes
   - o No

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

   - o Postoperative ileus
   - o Other (please explain) _____

4. I use compounded ipamorelin acetate 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 ipamorelin acetate.
   - o Other (please explain) _____

5. Do you stock non-patient-specific compounded ipamorelin acetate at your practice?

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

6. I obtain compounded ipamorelin acetate 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) _____

7. 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) _____

8. 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 2.2. Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk 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 utilize a 503B outsourcing facility to acquire compounded drugs?

   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

   - o I do not obtain any compounded drugs from 503B outsourcing facilities
   - o Amitriptyline / Ketoprofen / Oxymetazoline
   - o Budesonide
   - o Calcium gluconate
   - o Droperidol
   - o Epinephrine
   - o Epinephrine for ophthalmic administration
   - o Epinephrine / Lidocaine for ophthalmic administration
   - o Epinephrine / Bupivacaine / Fentanyl
   - o Fentanyl
   - o Flurbiprofen
   - o Flurbiprofen for ophthalmic administration
   - o Hydromorphone
   - o Ipamorelin
   - o Ketoprofen / Nifedipine
   - o Lidocaine / Epinephrine / Tetracaine HCl
   - o Meperidine
   - o Morphine
   - o Naloxone
   - o Neomycin
   - o Phentolamine
   - o Promethazine

- o Remifentanil
- o Sufentanil
- o Tramadol
- o None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

    - o Dental
    - o Dermatology
    - o Endoscopy
    - o Neurosurgery
    - o Obstetrics/gynecology
    - o Ophthalmology
    - o Otolaryngology
    - o Orthopedics
    - o Pain
    - o Plastics
    - o Podiatry
    - 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.