Summary Report

Phentolamine mesylate

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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
AUA	American Urological Association
EMA	European Medicines Agency
ED	Erectile dysfunction
EU	European Union
FDA	Food and Drug Administration
ICI	Intracavernosal injection
IRB	Institutional Review Board
OTC	Over-the-counter
PDE5I	Phosphodiesterase type 5 inhibitor
PGE1	Alprostadil or prostaglandin E1
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 phentolamine mesylate (UNII code: Y7543E5K9T), 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 phentolamine mesylate 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 phentolamine mesylate 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 phentolamine mesylate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Phentolamine mesylate was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA), Fagron, and Specialty Sterile Pharmaceutical Society (SSPS). Phentolamine mesylate was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Phentolamine mesylate was nominated for the following indications:

- Anesthesia reversal, dermal necrosis, erectile dysfunction (ED), extravasation, heart failure, hypertensive emergency, pheochromocytoma diagnosis, pheochromocytomectomy via a 0.5-2 mg/mL intravenous, intramuscular, subcutaneous, submucosal, and intracavernosal injection (ICI) in Trimix combination (alprostadil/papaverine/phentolamine).
- ED via a 5 mg/mL intramuscular or intravenous injection.
- Oral anesthesia reversal via a 5 mg/mL injection.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of phentolamine mesylate.[6-11]

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.

- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- According to SSPS, in order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Each year, 300 million cartridges of oral anesthetic are sold and used for dentistry practice. In many cases, patients do not need the local anesthesia for the entire length of time that commonly used anesthetics provide. OraVerse is a phentolamine injection specifically indicated as an oral anesthetic reversal. OraVerse is formulated with a sulfur-contained excipient. For patients allergic to sulfur, it is best to compound a phentolamine submucosal injection that does not include the sulfur component.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of phentolamine mesylate 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 phentolamine mesylate; name variations of phentolamine mesylate 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 phentolamine mesylate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: phentolamine, injectable administration, and alprostadil or papaverine (refer to Appendix 1 for full search strategies). Single-agent injectable products were not included in the literature review due to the availability of FDA-approved single-agent injectable phentolamine

mesylate products. Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited human studies in English language. Searches were conducted on April 4, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on April 4, 2020 for clinical practice guidelines that recommended the use of phentolamine and provided sufficient information on dosing and administration.

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

Study selection

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

- Phentolamine mesylate is available as an FDA-approved product in the nominated dosage form and ROA.
- Phentolamine mesylate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for phentolamine mesylate.
- Phentolamine mesylate is available in the nominated dosage form and ROA in Abu Dhabi and Canada.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Phentolamine mesylate	5 mg/vial; 0.4 mg/1.7 mL	Injectable	Injection	Prescription	3/11/1998

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date
Phentolamine mesylate	0.4 mg/1.7 mL	Solution	Submucosal	Canada	Prescription	9/17/2014
Phentolamine mesylate	5-10 mg/mL	Solution	Injection, intramuscular, intravenous	Abu Dhabi	Active	–
				Canada	Prescription	6/15/2001

Abbreviation: "– ", not mentioned.
[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.

Results of literature review

Study selection

Database searches yielded 975 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 681 titles and abstracts were screened. After screening, the full text of 166 articles was reviewed. Finally, 26 studies were included. One hundred forty studies were excluded for the following reasons: wrong study design (118 studies); phentolamine mesylate only mentioned briefly (9); wrong dosage form or ROA (5); unable to obtain (3); phentolamine mesylate not used clinically (2); used as brand or propriety product (1); duplicate study (1); wrong substance (1).

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

Characteristics of included studies

The 26 included studies were published between 1991 and 2020. There were 7 experimental studies, 11 observational studies, 8 descriptive studies, and 0 clinical practice guidelines. The 26 studies were conducted in the following countries: Brazil, Egypt, and US.

A total of 4522 patients participated in the 26 included studies. The number of patients in each study ranged from 1 to 1089.

Outcome measures differed among the included studies and included: erection rigidity strength, erectile function, duration of erection, percent tumescence, Doppler assessment, sexual satisfaction, side effects such as presence of intracorporeal fibrosis, plaque formation, or priapism, ICI compliance rating, patient-reported experience, frequency of injection use, resumption of unaided erection, number of injections required for sufficient erection, and erection requiring pharmacologic reversal.

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

Use of phentolamine mesylate

One thousand five hundred nine patients received phentolamine mesylate as a treatment for ED, administered via the intracavernosal and intracorporeal routes in doses ranging from 0.05 mL to 2 mL. In 3 studies of injectable phentolamine in combination with alprostadil and papaverine for the treatment of ED, the number of patients who received treatment was not specified.[12-14] Duration of treatment ranged from once to 81 months. Two hundred eighty-six patients received phentolamine mesylate for penile doppler testing and/or self-injection education, administered via the intracavernosal route in doses ranging from 0.1 mL to 1 mL. In 3 studies of injectable phentolamine in combination with alprostadil and papaverine for penile doppler testing/self-injection education, the number of patients who received treatment was not specified.[15,16] The duration of treatment was one time. Sixty-three patients received phentolamine mesylate for urologic evaluation for Peyronie's disease, administered via the intracavernosal route in doses ranging from 0.2 mL to 1 mL. The duration of treatment was one time.

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

Phentolamine mesylate was used as a compounded product, and it was used in a combination product (refer to Table 8 and 9).

In 16 studies, the authors' concluding statement recommended the use of Trimix for the treatment of ED.[13,14,17-30] In 2 studies, the authors' concluded that the use of Trimix was not recommended or further studies were necessary for the treatment of ED.[12,31] In 8 studies, the authors' concluding statements were not specific to phentolamine.[15,16,32-37]

Pharmacology and historical use

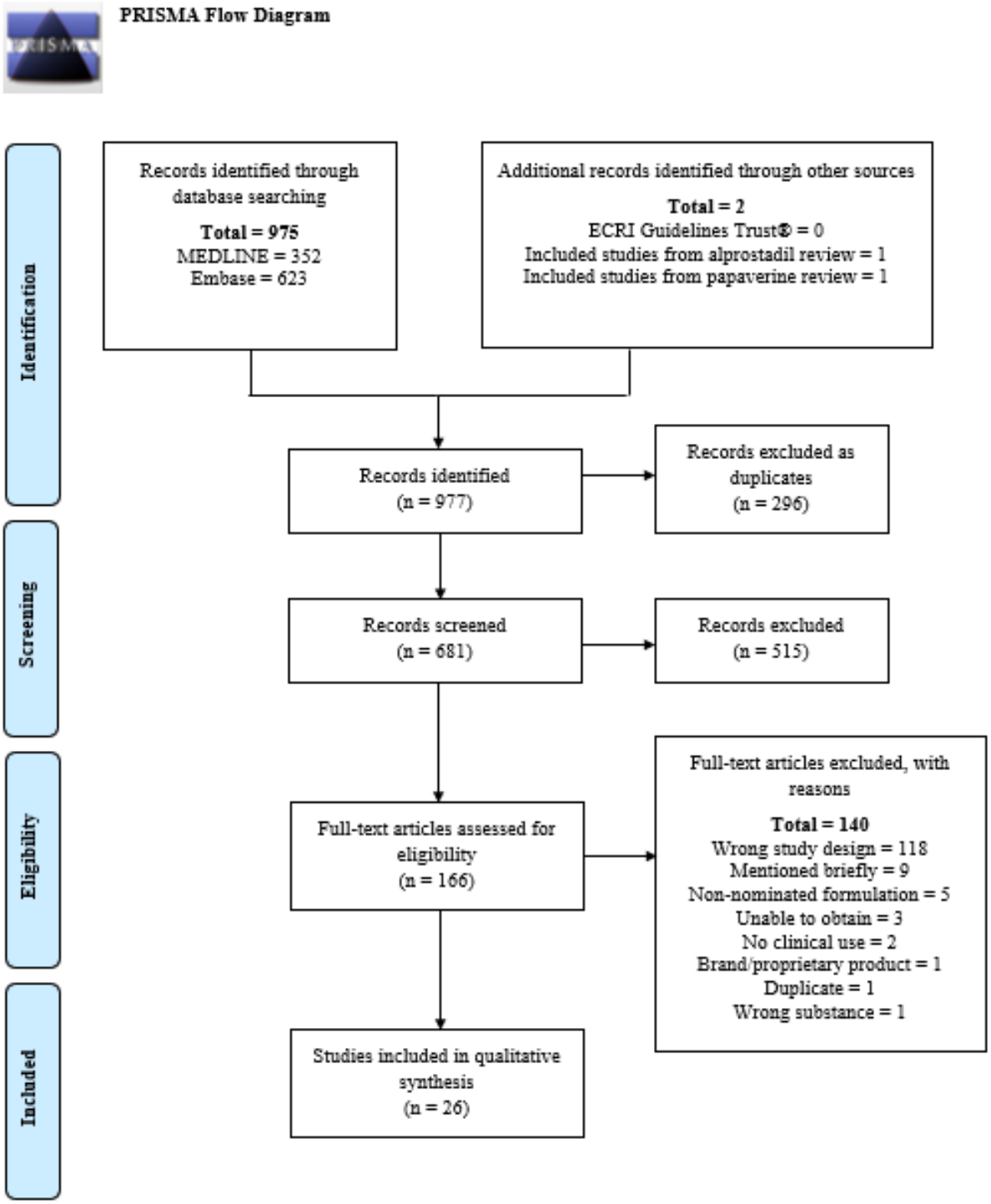
In addition to the 26 included studies, 10 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of phentolamine mesylate.

Phentolamine has been available in the US since 1952 for "clinical reversal of accidental extravasation of catecholamines during intravenous administration and for the diagnosis of pheochromocytoma."[8] In 2008, the FDA approved phentolamine for the "reversal of soft tissue anesthesia and the associated functional deficits resulting from a local dental anesthetic containing a vasoconstrictor."[8,10] After routine dental procedures, OraVerse® by Septodont Inc "has been found to accelerate the return of soft tissue feeling."[8] The FDA-approved product is not for use in children less than 6 years old or weighing less than 15 kg due to limited data supporting a favorable safety profile in this younger age population.[10]

ED is "an inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[38] According to the American Urological Association (AUA), oral phosphodiesterase type 5 inhibitors (PDE5Is) are first line for men with ED unless contraindicated.[39] For patients who have contraindications to using PDE5Is, prefer to not take an oral medication, or are getting an inadequate response from PDE5Is, they may consider using the ICI approach for ED.[39] Alprostadil (PGE1) is the only FDA-approved medication for ICI injection, and is the only medication that tends to be used as a single agent.[39] Phentolamine, papaverine, and atropine are three other medications with established efficacy for ED that are used in various combinations with one another and alprostadil.[39] Phentolamine, a non-selective alpha-adrenergic antagonist, inhibits smooth muscle contraction by a direct effect on the corpus cavernosum smooth muscle and blood vessels.[40] Because phentolamine has "weak efficacy as [a] single agent," it is used in combination therapy.[40]

Vasoactive ICI agents were first introduced in 1982.[41] Papaverine and phentolamine were the first to be used widely for ED treatment but "these unlicensed agents sometimes had significant side effects such as priapism and cavernosal fibrosis."[42] In 1986, the use of alprostadil for ED treatment and diagnosis was first reported, and in 1996, the FDA approved Caverject®, an alprostadil sterile powder formulation for injection.[41,42] In 1990, Trimix was popularized by Goldstein as an effective regimen for self-injection therapy.[43] Trimix is recommended to those who fail ICI monotherapy.[42] This combination enhances efficacy by acting synergistically, and allows for lower doses to be used, thus reducing the frequency of undesirable side effects.[44] Although ICIs have good clinical efficacy rates, "dropout rates [are] as high as 40-50% due to pain, priapism, penile fibrosis, hematoma, ecchymosis, or fear of the needle."[40,45] There is currently no combination therapy that is globally approved; many of the combinations are formulated by compounding pharmacies leading to "variations in constituents and consistencies among such therapies."[40] The compounded products must be refrigerated and used within 30 days due to the rapid degradation of PGE1.[43] Cost may be another factor for consideration in the treatment of ED. The compounded injectable agents can be less costly than FDA-approved products, but insurance does not always cover compounded products.[13,17]

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[15,16,18-20,25,27,36]	8
Experimental[12,14,23,28,32,33,35]	7
Observational[13,17,21,22,24,26,29-31,34,37]	11

Table 4. Number of studies by country

Country	**Number of Studies**
Egypt[23,33,35]	3
US[12-22,24-32,36,37]	22
Multiple Countries • Brazil and US[34]	1
	Total US[a]: 23 Total Non-US Countries[a]: 4

[a]Study 34 counted in both US and non-US total

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Indication 1: Erectile dysfunction (ED)					
Albaugh and Ferrans, 2010, US[17]	One-group, pretest/posttest design	20 Men who had prostatectomy for prostate cancer (100%, mean 58 y ± 8.8)	• Papaverine/phentolamine (2) • Trimix (11) • Edex/PGE1 (7)	Erection rigidity strength, erectile function via the International Index of Erectile Function (IIEF), self-esteem and relationship questionnaire, erectile dysfunction inventory of treatment satisfaction, injection self-efficacy scale – all before, 1 month, and 3 months after initiation of ICI therapy	Penile injections for ED after radical prostatectomy were an effective treatment option and associated with improved satisfaction with the sexual relationship and improved sexual confidence and self-esteem.
Allen *et al*, 1992, US[12]	Double-blind, crossover study	7 Men with organic impotence (100%, age not mentioned)	• Papaverine/phentolamine (7*) • Trimix (not specified) • Papaverine/PGE1 (not specified) *Each patient received 2 injections per test date. All were given papaverine/phentolamine and then given either papaverine/PGE1 or Trimix	Duration of erection, maximum rigidity	The combination of papaverine with PGE1 produces longer duration erections than papaverine with phentolamine. There is no additional benefit gained by adding phentolamine to papaverine with PGE1.
Bennett *et al*, 1991, US[18]	Case series	116 Impotent patients (100%, range 30-75 y)	• Trimix (116)	Percent tumescence, Doppler assessment	The Trimix combination of papaverine, phentolamine, and PGE1 is effective and safe for a self-administered pharmacological treatment program.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Bernie *et al*, 2017, US[13]	Prospective	175 Patients enrolled in the ICI program Group 1 empiric (100%, mean 61.9 y ± standard error of the mean 1.4) Group 2 risk-based (100%, mean 61.3 y ± standard error of the mean 0.7)	• Group 1 empiric* (57) • Group 2 risk-based**(118) *Patients treated irrespective of ED etiology or severity. Initial is PGE1 only then PGE1/phentolamine or a low dose Trimix. **Patients treated with papaverine and phentolamine, low dose Trimix or a high dose Trimix using an algorithm factoring ED etiology and risk factors.	IIEF-erectile function domain, quality of erection questionnaire, sexual quality of life, erectile dysfunction inventory of treatment satisfaction at baseline, 3, and 6 months after initiation of therapy	Both treatment strategies resulted in significant improvements across multiple domains of sexual function. The complication rates, satisfaction, and efficacy overall were similar in both.
Chao and Clowers, 1994, US[19]	Case series	35 Patients with neurogenic ED (100%, range 22-59 y)	• Trimix (35)	Presence of intracorporeal fibrosis or plaque formation, rigid erection lasting 1-2 hours	Intracavernous Trimix injection is a "satisfactory, cost-effective method to [achieve] erection without significant side effects."
Davis *et al*, 2009, US[32]	Randomized, phase II open label study	107 Patients with prostate cancer recommended for unilateral nerve-sparing radical prostatectomy Control group (100%, mean 55.3 y ± 6.1) Sural nerve graft group (100%, mean 57.3 y ± 4.8)	• Control group (41) • Sural nerve graft (66) At postoperative week 6, all patients had a treatment plan that included sildenafil, a vacuum erection device, and ICI therapy with Trimix.	Patient completed quality of life questionnaires, assessment of penile rehabilitation compliance, side effects, intracavernous injection compliance rating (good, poor, or none)	Unilateral sural nerve graft with radical prostatectomy compared to unilateral sural nerve graft alone did not increase potency rate at 2 year following surgery. "Secondary endpoints also did not show an improvement in time to potency or urinary function at 1 [year]. Based upon the power of this study, we cannot exclude a smaller benefit."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Govier *et al*, 1993, US[20]	Case series	Part 1: 170 Patients with ED (100%, age not specified) Part 2: 146 Patients with ED (100%, range 24-85 y) Part 1: Patients learn how to perform injection and to establish the effective dose for the patient. Part 2: Of the original 170, only 146 patients want to continue the treatment program.	• Trimix (170)	Functional erection and side effects	"In summary, while the perfect injectable agent for a pharmacological erection program does not exist, triple-drug therapy has many positive features. Its superior smooth muscle relaxation and dose response, low incidence of pain and low incidence of scarring make it a viable first line agent for patients in a pharmacological erection program."
Gupta *et al*, 1997, US[21]	Retrospective chart review	1089 ED patients total Active group (100%, range 21-91 y) Inactive group (100%, range 22-94 y)	• PGE1 (636) • Papaverine/PGE1 (21) • Papaverine/phentolamine (143) • Trimix (222)	Patient-reported experience, physical exam, and frequency of injection use	There was a high satisfaction rate for the use of PGE1. "Failure with [PGE1] and triple drug therapy is a likely predictor of failure of intracavernous injection. Remaining in the program past a critical period of approximately 2 months is a probable predictor of long-term success, confirming intracavernous injection as an effective long-term option."
Hsiao *et al*, 2011, US[24]	Cohort	122 Patients who were prescribed ICI for ED treatment for at least 6 months (100%, mean 68 y ± 32)	• Trimix (122)	Change in scores in satisfaction domains of IIEF; type of injection used; predictors of satisfaction	"While over a third of patients had stopped ICI at the time of follow-up, those that continued to inject had high levels of satisfaction as measured by the IIEF, the gold standard for the evaluation of erectile function."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Katlowitz *et al*, 1993, US[25]	Case series	25 Patients with suspected vasculogenic impotence (100%, range 36-72 y)	• PGE1 (11) • Trimix (14)	Arterial diameter, peak systolic flow and end-diastolic flow on Doppler ultrasound, and grade of erection	"Our data indicate that a patient who fails intracavernosal injection in the office setting should not be immediately excluded from a pharmacologic erection program because adequate erection may be achieved after injection by the addition of audiovisual sexual stimulation."
Lauer, 2018, US[14]	–	21 Patients with spinal cord injury and ED (100%, age not mentioned)	• Trimix • PGE1 Number of patients not specified for either intervention	Sexual satisfaction score and Sexual Health Inventory of Men questionnaire	Both ED and sexual satisfaction in spinal cord injured males were improved via penile injections. Penile injections are a clinically effective intervention.
Maniam *et al*, 2001, US[31]	Retrospective study	19 Patients with organic ED (100%, mean 53.47 y ± 9.96)	• PGE1 (7) • Trimix (12)	Nocturnal penile tumescence testing parameters via number of erectile episodes, base and tip tumescence, percent of time with rigidity greater than 70% at the penile base and tip	The data implies that there is subjective improvement that develops in some men after long-term ICI, but there is no objective improvement in spontaneous erectile function as measured by nocturnal penile tumescence testing.
Marshall *et al*, 1994, US[26]	–	45 Patients (100%, mean 58.7 y ± 8)	• PGE1 (21) • Trimix (14) • Control (10)	Doppler ultrasound study (cavernous artery diameter and peak flow) before and after long-term ICI therapy	"In this study, we have shown that long-term intracavernous therapy with vasoactive substances leads to significantly improved blood flow in the cavernous artery. This may represent a medication induced improvement in the efficiency of the sinusoidal and arteriolar smooth muscle."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
McCullough *et al*, 2020, US[27]	Case report	1 ED patient (100%, 52 y)	• Trimix (1)	Erection hardness	"[Computed tomography] cavernosography is useful in determining the site of venous leak in mean with ED and aids in the therapeutic decision making and patient education."
Miranda *et al*, 2015, Brazil and US[34]	Cohort	476 Patients who had radical prostatectomy and on penile injection therapy (100%, mean 62 y ±14)	• Trimix (476)	Rate of priapism	There was no difference in rate of priapism between tadalafil and sildenafil users. For men on tadalafil, the mean Trimix dose was higher and a higher proportion of those on tadalafil experienced a prolonged erection not requiring an emergency room visit. Both strategies with tadalafil and sildenafil appear to be safe in the penile injection population, but excellent patient counseling is required, especially for those using tadalafil.
Mullhall *et al*, 2005, US[28]	Nonrandomized study	132 Patients with clinically organ-confined prostate cancer, who had fully functional erection by self-report and who were scheduled to undergo radio prostatectomy surgery (100%, mean 59 y ± 10.6)	• Rehabilitation* group (58) • No rehabilitation group - no erectogenic medication treatments (74) *Pursued pharmacologic penile rehabilitation-protocol is initial challenge with sildenafil. If sildenafil fails, then ICI Trimix therapy used.	Capability of having medication-unassisted intercourse, mean erectile rigidity, mean IIEF erectile function domain scores, percentage of patients responding to sildenafil, the time to become a sildenafil responder, and the percentage of patients responding to ICI therapy	A pharmacologic penile rehabilitation protocol results in higher rates of spontaneous functional erections and erectogenic drug response after radical prostatectomy.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Nandipati *et al*, 2006, US[30]	Non-randomized prospective study	22 Patients who underwent bilateral nerve-sparing radical prostatectomy (100%, mean 58.3 y ± 6.9)	• PGE1 (18) • Low dose Trimix (4)	Sexual activity, abridged version of IIEF questionnaire, penile doppler studies at 3 and 6 months	"Early injections facilitate early sexual intercourse, patient satisfaction and potentially early return of spontaneous erections. Combination therapy with sildenafil allows lower dose of intracavernous injections, which decreases the discomfort."
Raina *et al*, 2003, US[22]	Retrospective study	102 Patients who had radical prostatectomy (100%, mean 60.4 y ± 6.3)	• PGE1 (62) • Low dose Trimix (21) • High dose Trimix (19)	Sexual Health Inventory of Men scores, IIEF scores, treatment effect, frequency of use, duration of erection	"This study suggests that intracorporeal injections are an excellent salvage option in nerve sparing patients who fail oral therapy and a first option in patients with non-nerve sparing procedures."
Salem and Mostafa, 2012, Egypt[23]	–	176 Patients with organic erectile dysfunction (100%, age not specified)	• Trimix (56) • Sildenafil (55) • Vacuum constrictive device (54)	Resumption of unaided erection, mean peak systolic velocity, mean cavernosal artery diameter	"It is concluded that repeated regular use of ICI, sildenafil or [vacuum constrictive device] by patients with organic ED has a positive impact on their cavernous blood flow and erectile activity."
Shamloul *et al*, 2004, Egypt[33]	Double-blind comparative study	50 Patients with ED (100%, mean 47.2 y ± 3.4)	• Group A – in-office Bimix (papaverine and phentolamine) ICI, 1-week later papaverine and chlorpromazine ICI (20) • Group B – in-office Trimix ICI, 1-week later papaverine, PGE1, and chlorpromazine (20) • Group C – various chlorpromazine ICI (10)	Erectile response	Chlorpromazine is similar to phentolamine's efficacy and short-term side effect profile. It can be used as an intracavernous vasoactive agent.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Von Heyden *et al*, 1993, US[29]	Retrospective analysis	101 Patients who received ICI as primary therapy for vasculogenic impotence (100%, range 22-80 y)	• PGE1 (70) • Trimix (31)	Ultrasound of the penis, quality of erection on graded scale	"We believe that an erection longer than 30 to 60 minutes carries an increased risk of priapism. By diminishing the dose of intracavernous agent necessary for home injection, the combined intracavernous injection and self-stimulation test markedly decreases this risk. Although occasionally a patient may find a request for genital self-stimulation to be embarrassing, in our experience most patients cooperate fully once the rationale for self-stimulation is explained to them. That rationale is to initiate and maintain a natural erection adequate for sexual satisfaction without adverse effects. This is the preferred outcome of our self-injection program."
Indication 2: Penile Doppler testing/self-injection education					
Avant *et al*, 2017, US[37]	Retrospective chart review	262 Men undergoing penile duplex doppler ultrasound for ED evaluation (100%, mean age provided only 53 y)	• Trimix (262)	Number of injections required for sufficient erection, IIEF-6 score	During penile duplex doppler ultrasound, patients with lower IIEF scores coronary disease, and diabetes mellitus may need higher volumes of erectogenic medications. "This information may help to create standardized and efficient protocols for repeated dosing regimens."
Clemens *et al*, 2011, US[15]	Case series	919 Patients who underwent diagnostic penile injection (100%, mean age provided only 56.7 y)	• PGE1 • Trimix Number of patients in each group not mentioned	Prolonged erection and priapism requiring reversal	Erections induced by ICI for office diagnostic procedures come with a significant risk of prolonged erection. Early pharmacologic reversal at one hour can effectively prevent prolonged erection and priapism.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Clemens *et al*, 2012, US[16]	Case series	243 Patients who had pharmacologic erection reversal after diagnostic injection for penile doppler testing (100%, range 24-88 y)	• PGE1 • Trimix Number of patients in each group not mentioned, but authors mention most of the men were injected with PGE1	Erection requiring pharmacologic reversal	Pharmacologic reversal at 1-2 hours is a "safe, effective practice that prevents priapism, minimizes patient discomfort and embarrassment, and improves practice efficiency."
Ghanem *et al*, 2016, Egypt[35]	Randomized and controlled study	24 Patients with vascular ED (100%, age not mentioned)	• Treatment group – Botulinum toxin type A injection (12) • Control group – saline injection (12) All patients given Trimix solution for the penile doppler study	Erection hardness score	For treatment of vascular ED patients resistant to other non-surgical treatment options, there is a possible benefit of intracavernosal botulinum toxin type A injection.
Indication 3: Urologic evaluation for Peyronie's disease					
McCullough *et al*, 2020, US[36]	–	63 Patients under consideration for treatment of Peyronie's Disease (100%, mean age provided only 57 y)	• Trimix (63)	Erection hardness score	The extent and severity of Peyronie's disease may be underestimated at the time of presentation and initial evaluation. In particular, the corporal involvement can be incompletely assessed by conventional diagnostic modalities. These abnormalities may be more clearly defined by using computed tomography cavernosography.

Abbreviations: "–", not mentioned; ED, erectile dysfunction; ICI, intracavernosal injection; IIEF, International Index of Erectile Function; PGE1, alprostadil or prostaglandin E1.

[a]As defined by authors.

[b]Alprostadil is also known as prostaglandin 1 (PGE1); for accuracy, the substance name that the study authors used is presented in this table.

[c]Trimix is a combination of alprostadil, papaverine, and phentolamine.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Erectile dysfunction[12-14,17-22,24-32,34]	0.0.5-1 mL/1-12 times a month	0.59 mcg/mL – 5 mg/mL	Solution	Intracavernosal, intracorporeal	Once – 81 months
Penile Doppler testing/self-injection education[15,16,37]	0.1-1 mL	1 mg/mL	Solution	Intracavernosal	–
Urologic evaluation for Peyronie's disease[36]	0.2-1 mL	2 mg/mL	Solution	Intracavernosal	Once

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Erectile dysfunction[23,33,34]	0.5-2 mL	1 mg/mL	Solution	Intracavernosal	Once – 3 months
Penile doppler testing[35]	–	1 mg	Solution	Intracavernosal	Once

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Alprostadil 5 mcg/mL-500 mg/mL / Papaverine 17.65 mcg/mL -30 mg/mL / Phentolamine 0.59 mcg/mL -5 mg/mL – injection[12-37]	26

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Erectile dysfunction[24,30]	2006-2011	Purchased from a compounding pharmacy[24]	Solution	–
		Not mentioned, "this mixture is purchased from the hospital pharmacy."[30]		Alprostadil 5.88 mcg/mL / Papaverine 17.65 mg/mL / Phentolamine 0.59 mg/mL

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Seven SMEs discussed phentolamine mesylate. Amongst these 7 SMEs, there were 6 medical doctors and 1 regulatory specialist. The SMEs specialized and/or were board-certified in andrology, anesthesiology, sexual/reproductive health, and urology, working in academic medical centers, hospital/health systems, pharmacy/pharma companies, and private practice/clinics. The SMEs had been in practice for 8 to 33 years.

For the treatment of ED, the patient is usually first given a PDE5I such as Cialis® (tadalafil), Levitra® (vardenafil), Stendra® (avanafil), or Viagra® (sildenafil citrate) unless they are unable to take PDE5Is due to contraindications or unable to tolerate side effects. If a PDE5I fails, then most patients will go on Trimix (alprostadil/papaverine/phentolamine) ICI therapy. Although Trimix is typically the go to, there are also other variations, such as Bimix and Quadmix. One SME added that PDE5Is usually do not work in patient populations who have more severe ED due to a severe corpus venous leak such as: severe diabetics with a very high hemoglobin A1c; patients who are 3-6 months post-vasectomy; post-radical cystectomy; or a history of any pelvic surgery with neurogenic ED as the underlying cause. However, a trial of PDE5Is should still be given. If the injections do not work, then a penile implant would be the next option. One SME also provided some background about the ED drugs, stating that Trimix has been used since the early 1990s, before PDE5Is. Sildenafil citrate and tadalafil were approved in 1998.

All the SMEs who specialized in urology used Trimix. Trimix is a "staple of treatment for severe ED," and is in the AUA guidelines for ED. Caverject® and edex®, both alprostadil products for injection, are FDA-approved drugs that use a higher volume for injection, but they do not work as well as Trimix. Several SMEs commented that injecting alprostadil alone can cause pain and/or burning, especially when used at higher doses. The Trimix combination works synergistically and the side effects such as pain and burning are lessened because of the lower alprostadil dose. One SME stated the only time they used the commercially available alprostadil injection is when they have a patient who travels a lot and they are unable to keep Trimix refrigerated. The SME preferred to start with Trimix, and scale back with dose adjustments or other mixes as needed because patients who have failed oral PDE5Is usually have severe ED. For patients in which a PDE5I is efficacious but is intolerable due to side effects, Bimix can be considered. If the patient is started on a single agent ICI with an associated side effect and fail that, "[the patient's] confidence [for] using any other injection [therapy] goes down dramatically." There is one SME who expressed that most people do not want to use an injection, especially in a sensitive area. One SME added that 65-70% of patients will respond to the injections, which is the same response rate as PDE5Is. The reason patients do not respond to PDE5Is is usually because their disease is severe.

A few SMEs also commented about the cost of these ED drugs. One stated that until 2 years ago when sildenafil citrate and tadalafil became generic, compounded ICIs were less expensive than PDE5Is so there were some patients who used compounded ICI for financial reasons. An SME also commented that they think the commercially available injection products are expensive.

All the SMEs use compounded ICIs; some SMEs specified that they obtain them from a 503A compounding pharmacy. There was also a 503B who stated that they have compounded Trimix. One SME mentioned that they do stock Trimix in their office to use when conducting penile Dopplers to evaluate blood flow. For patient specific prescriptions, one SME stated that the injection is ordered, compounded, and then shipped to that patient's house. The patient then brings the compounded product to their office to teach the patient how to use the injection and to monitor the patient's response. The patient is also given specific instructions on the dose to use at home and how to increase the dose. The potential concerns with a patient using the injection incorrectly include priapism, nerve damage, bleeding,

and hematomas; however, this SME has not encountered these issues because they have shown the patients the proper administration technique.

Anesthesiology SMEs were unfamiliar with or did not use phentolamine. One SME commented that phentolamine is used for partial reversal. This SME thought this would be more applicable to dentists. Another SME, who had never used phentolamine, thought it would be for people with hypertensive crisis in pheochromocytoma operation. For vasodilation, this SME would instead use hydralazine, nitroglycerin, or nitroprusside.

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 Nurse Practitioners in Women's Health (NPWH) organization; 96 people responded to this survey (refer to Table 11 for respondent characteristics and Appendix 2.2 for survey instrument).

Among respondents, 1 (1%) used alprostadil/papaverine/phentolamine in combination as a compounded product. The 1 respondent who used alprostadil/papaverine/phentolamine as a combination product did not provide the dosage form or ROA that they prescribed or administered, nor did the respondent provide the indication for which they prescribed or administered this combination (refer to Table 12).

The 1 respondent did not provide a reason for using alprostadil/papaverine/phentolamine as a compounded product versus using a commercially available product (refer to Table 13).

The 1 respondent who used compounded alprostadil/papaverine/phentolamine as a combination product did stock non-patient-specific compounded alprostadil/papaverine/phentolamine at their practice. The respondent obtained this combination product by compounding it themselves at their practice. Refer to Table 14 for how respondent obtained compounded alprostadil/papaverine/phentolamine.

A separate survey was also distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.3 for survey instrument).

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 phentolamine from a 503B outsourcing facility (refer to Table 15).

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 16).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=96)
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Master of Science (MS)	1
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	95
Physician Assistant (PA)	0
Practice Setting	**Responses, n (N=96)[a]**
Physician office or private practice	47
Outpatient clinic	29
Hospital or health system	9
Academic medical center	7
Emergency room	0
Operating room	1
Other[b]	3

[a]Some respondents reported more than one practice setting.
[b]Responses to other: retired from research; Graduate Education Program faculty; "recently moved to FL."

Table 12. Conditions for which alprostadil/papaverine/phentolamine prescribed or administered

Condition	Responses, n (N=1)[a]
Female sexual arousal disorder	0
Other	0
None of the above	1

[a]Out of 96 respondents, 1 reported prescribing or using compounded alprostadil/papaverine/phentolamine as a combination product.

Table 13. Reasons for using compounded alprostadil/papaverine/phentolamine

Reason	Responses, n (N=1)[a]
Commercial product not available in desired dosage form, strength, or combination	0
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	0
No commercial products	0
Other – no explanation provided	1

[a]Out of 96 respondents, 1 reported prescribing or using compounded alprostadil/papaverine/phentolamine as a combination product.

Table 14. Use of non-patient-specific compounded alprostadil/papaverine/phentolamine

Do you stock non-patient-specific compounded alprostadil/papaverine/phentolamine at your practice?	**Responses, n (N=1)[a]**
Yes	1
No	0
Not sure	0
How do you obtain compounded alprostadil/papaverine/phentolamine?	
Compound yourself at practice	1
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	0
Purchase from outsourcing facility	0
Other	0

[a]Out of 96 respondents, 1 reported prescribing or using compounded alprostadil/papaverine/phentolamine as a combination product.

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

Phentolamine mesylate was nominated for inclusion on the 503B Bulks List for anesthesia reversal, dermal necrosis, ED, extravasation, heart failure, hypertensive emergency, oral anesthesia, pheochromocytoma diagnosis, pheochromocytomectomy via a 0.5-2 mg/mL intravenous, intramuscular, subcutaneous, submucosal, and ICI in Trimix combination and alone as a 5 mg/mL intramuscular or intravenous injection. Phentolamine mesylate is available in the nominated form and ROA in Abu Dhabi, Canada, and US.

From the literature review and interviews conducted, phentolamine is used for ED. Other indications mentioned from the literature include diagnosis of pheochromocytoma, penile doppler testing/self-injection education, soft tissue anesthesia, reversal of extravasation of catecholamines, and urologic evaluation for Peyronie's disease. The current treatment for ED includes a PDE5I, Trimix injection, or a penile implant.

All the SMEs who specialized in urology used Trimix. Trimix is a "staple of treatment for severe ED," and is in the AUA guidelines for ED. Several SMEs commented that injecting alprostadil alone can cause pain and/or burning, especially when used at higher doses. The Trimix combination works synergistically and the side effects, such as pain and burning, are lessened because of the lower alprostadil dose. One SME stated the only time they used the commercially available alprostadil injection is when they have a patient who travels a lot and is unable to keep Trimix refrigerated. All the SMEs use compounded ICIs; some SMEs specified that they obtain it from a 503A compounding pharmacy, and one mentioned that they stock Trimix in their office to use when conducting penile Dopplers. There was also a 503B who stated that they have compounded Trimix. Patients are taught in office how to use the ICI therapy.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Among the 96 respondents to the NPWH survey, 1 (1%) used alprostadil/papaverine/phentolamine in combination as a compounded product. The 1 respondent who used alprostadil/papaverine/phentolamine as a combination product did not provide the dosage form or ROA that they prescribed or administered, nor did the respondent provide the indication for which they prescribed or administered this combination. The 1 respondent who used compounded alprostadil/papaverine/phentolamine as a combination product did stock non-patient-specific compounded alprostadil/papaverine/phentolamine at their practice. The respondent obtained this combination product by compounding it themselves at their practice.

Two hundred thirty people responded to the survey distributed via the ASCA. One respondent reported obtaining phentolamine from a 503B outsourcing facility.

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45. Anaissie J, Hellstrom WJ. Clinical use of alprostadil topical cream in patients with erectile dysfunction: a review. *Research & Reports in Urology.* 2016;8:123-131.

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 April 3, 2020
- Date last searched: April 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 352

1	phentolamine/	9012
2	fentolamin$.tw.	16
3	pentholamin$.tw.	2
4	pentolamin$.tw.	6
5	phentolamin$.tw.	9401
6	or/1-5	13658
7	exp administration, intravenous/	142112
8	infusions, parenteral/	26205
9	injections/	42275
10	inject$.tw.	730933
11	infusion$.tw.	242365
12	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12047
13	intravenous$.tw.	336090
14	intra venous$.tw.	571
15	intravascular$.tw.	47075
16	intra vascular$.tw.	297
17	intracaverno?s$.tw.	3599
18	intra caverno?s$.tw.	88
19	intraspongiosal$.tw.	5
20	intra spongiosal$.tw.	0

21	or/7-20	1261854
22	alprostadil/	6905
23	papaverine/	5870
24	drug combinations/	72459
25	al?prostadil$.tw.	674
26	pge 1.tw.	649
27	pge1.tw.	5488
28	pge1alpha.tw.	1
29	prostaglandin$ e 1.tw.	792
30	prostaglandin$ e1.tw.	7153
31	prostaglandin e1alpha.tw.	5
32	papaverin$.tw.	5169
33	trimix.tw.	129
34	tri mix.tw.	5
35	(triple adj2 (therapy or treat$)).tw.	9039
36	bimix.tw.	14
37	bi mix.tw.	2
38	or/22-37	101868
39	and/6,21,38	530
40	exp animals/ not humans/	4686014
41	39 not 40	439
42	limit 41 to english language	352

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 623

1	phentolamine'/de	25191
2	fentolamin*':ti,ab,tn	17
3	pentholamin*':ti,ab,tn	2
4	pentolamin*':ti,ab,tn	17
5	phentolamin*':ti,ab,tn	11357
6	#1 OR #2 OR #3 OR #4 OR #5	26547
7	parenteral drug administration'/de	2118
8	intravenous drug administration'/exp	392156
9	intracavernous drug administration'/de	728
10	injection'/exp	247460
11	inject*':ti,ab	1085123
12	infusion*':ti,ab	353320
13	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18137
14	intravenous*':ti,ab	483246
15	intra venous*':ti,ab	1437
16	intravascular*':ti,ab	67223
17	intra vascular*':ti,ab	678
18	intracaverno$s*':ti,ab	5055
19	intra caverno$s*':ti,ab	189
20	intraspongiosal*':ti,ab	13
21	intra spongiosal*':ti,ab	1
22	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1994120

23	prostaglandin e1'/de	19638
24	papaverine'/de	14439
25	drug combination'/de	145988
26	al$prostadil*':ti,ab,tn	1359
27	pge 1':ti,ab,tn	193
28	pge1':ti,ab,tn	1973
29	pge 1alpha':ti,ab,tn	1
30	prostaglandin* e 1':ti,ab,tn	234
31	prostaglandin* e1':ti,ab,tn	2850
32	prostaglandin* e1alpha':ti,ab,tn	0
33	papaverin*':ti,ab,tn	7356
34	trimix':ti,ab	218
35	tri mix':ti,ab	15
36	(triple NEAR/2 (therap* OR treat*)):ti,ab	16260
37	bimix':ti,ab	29
38	bi mix':ti,ab	3
39	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	196266
40	#6 AND #22 AND #39	960
41	[animals]/lim NOT [humans]/lim	6013410
42	#40 NOT #41	773
43	#40 NOT #41 AND [english]/lim	623

Appendix 2.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded alprostadil / papaverine HCl / phentolamine. 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 alprostadil / papaverine HCl / phentolamine to your patients?

   - o Yes
   - o No

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

   - o Topical cream
   - o Topical gel
   - o Topical lotion
   - o Topical solution
   - o None of the above

4. I prescribe or administer alprostadil / papaverine HCl / phentolamine for the following conditions or diseases: (check all that apply)

   - o Erectile dysfunction
   - o Other (please explain) _____

5. I use compounded alprostadil / papaverine HCl / phentolamine 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 alprostadil / papaverine HCl / phentolamine.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded alprostadil / papaverine HCl / phentolamine at your practice?

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

7. I obtain compounded alprostadil / papaverine HCl / phentolamine 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 2.2. Survey instrument for Nurse Practitioners in Women's Health

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,

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Principal Investigator
The University of Maryland School of Pharmacy

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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. Which of the following compounded drugs do you prescribe or administer to your patients? (please check all that apply)
   - o Alprostadil as a solo product
   - o Alprostadil/Papaverine/Phentolamine as a combination product
   - o Aminophylline
   - o Anastrozole as a solo product
   - o Anastrozole/Testosterine as a combination product
   - o Oxytocin in combination with sildenafil citrate or tadalafil
   - o None of the above

4. Do you prescribe or administer alprostadil as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
   - o Topical cream, lotion, gel and/or solution
   - o Other (please explain) _____
   - o None of the above

5. I prescribe or administer alprostadil as a single agent product for the following conditions or diseases: (please check all that apply)
   - o Female sexual arousal disorder
   - o Other (please explain) _____
   - o None of the above

6. I use compounded alprostadil as a single agent product because: (please 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 alprostadil.
    - o Other (please explain) _____
7. Do you stock non-patient-specific compounded alprostadil as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure
8. I obtain compounded alprostadil as a single agent product from the following: (please 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) _____
9. Do you prescribe or administer alprostadil / papaverine / phentolamine as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Topical cream, lotion, gel and/or solution
    - o Other (please explain) _____
    - o None of the above
10. I prescribe or administer alprostadil / papaverine / phentolamine as a combination product for the following conditions or diseases: (please check all that apply)
    - o Female sexual arousal disorder
    - o Other (please explain) _____
    - o None of the above
11. I use compounded alprostadil / papaverine / phentolamine as a combination product because: (please 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 alprostadil / papaverine / phentolamine.
    - o Other (please explain) _____

12. Do you stock non-patient-specific compounded alprostadil / papaverine / phentolamine as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure

13. I obtain compounded alprostadil / papaverine / phentolamine as a combination product from the following: (please 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) _____

14. Do you prescribe or administer aminophylline as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o IV injection
    - o Oral liquid
    - o Oral capsules
    - o Topical cream, gel and/or ointments
    - o Other (please explain) _____
    - o None of the above

15. I prescribe or administer aminophylline as a single agent product for the following conditions or diseases: (please check all that apply)
    - o Orgasmic dysfunction
    - o Other (please explain) _____
    - o None of the above

16. I use compounded aminophylline as a single agent product because: (please 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 aminophylline.
    - o Other (please explain) _____

17. Do you stock non-patient-specific compounded aminophylline as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure

18. I obtain compounded aminophylline as a single agent product from the following: (please 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) _____
19. Do you prescribe or administer anastrozole as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Subcutaneous or subdermal pellet
    - o Other (please explain) _____
    - o None of the above
20. I prescribe or administer anastrozole as a single agent product for the following conditions or diseases: (please check all that apply)
    - o Hormone replacement
    - o Other (please explain) _____
    - o None of the above
21. I use compounded anastrozole as a single agent product because: (please 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 anastrozole.
    - o Other (please explain) _____
22. Do you stock non-patient-specific compounded anastrozole as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure
23. I obtain compounded anastrozole as a single agent product from the following: (please 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) _____
24. Do you prescribe or administer anastrozole / testosterone as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Subcutaneous or subdermal pellet
    - o Other (please explain) _____
    - o None of the above

25. I prescribe or administer anastrozole / testosterone as a combination product for the following conditions or diseases: (please check all that apply)
    - o Hormone replacement
    - o Other (please explain) _____
    - o None of the above

26. I use compounded anastrozole / testosterone as a combination product because: (please 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 anastrozole / testosterone.
    - o Other (please explain) _____

27. Do you stock non-patient-specific compounded anastrozole / testosterone as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure

28. I obtain compounded anastrozole / testosterone as a combination product from the following: (please 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) _____

29. Do you prescribe or administer oxytocin with sildenafil or tadalafil as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Oral or sublingual troche
    - o Intravenous or intramuscular injection
    - o Other (please explain) _____

30. I prescribe or administer oxytocin with sildenafil or tadalafil as a combination product for the following conditions or diseases: (please check all that apply)
    - o Increase female orgasm intensity
    - o Induction of labor
    - o Postpartum hemorrhage
    - o Adjunct for induced abortion
    - o Other (please explain) _____

31. I use compounded oxytocin with sildenafil or tadalafil as a combination product because: (please 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 oxytocin with sildenafil or tadalafil.
    - o Other (please explain) _____
32. Do you stock non-patient-specific compounded oxytocin with sildenafil or tadalafil as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure
33. I obtain compounded oxytocin with sildenafil or tadalafil as a combination product from the following: (please 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) _____
34. What is your practice setting? (please 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 explain) _____
35. What degree do you hold? (please check all that apply)
    - o Nurse Practitioner (NP)
    - o Other (please explain) _____

Appendix 2.3. 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,

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Principal Investigator
The University of Maryland School of Pharmacy

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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

- Tramadol
- None of the above

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

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