Summary Report

Anastrozole

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946

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January 2021

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

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
ASCO	American Society of Clinical Oncology
AI	Aromatase inhibitor
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 anastrozole (UNII code: 2Z07MYW1AZ), 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 anastrozole 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 anastrozole 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 anastrozole 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

Anastrozole was nominated for inclusion on the 503B Bulks List by AnazaoHealth and David Smith. Anastrozole was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Anastrozole was nominated for hormone replacement, to prevent the conversion of excess testosterone into estrogen/estradiol in female patients with a history of breast cancer and men treated with testosterone replacement therapy, via a 4 mg and 8 mg subcutaneous and subdermal pellet.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of anastrozole.[6-27]

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

- FDA-approved, commercial product is only available as an oral tablet; an implantable pellet form requires utilization of a bulk drug substance for accurate dosing and removing the oral tablet excipients.
- There is no FDA-approved product that is in a pellet form in combination with testosterone.
- Compounded products are requested to meet the individual needs of prescriber's patients.
- 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.
- Finished dosage forms may have considerable variance; using the bulk is more accurate.
- There may be patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of anastrozole 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 anastrozole; name variations of anastrozole 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 anastrozole. 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: anastrozole, subdermal pellet, and therapeutic use for nominated indication or substance nominated for use in combination (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 9, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 9, 2020 for clinical practice guidelines that recommended the use of anastrozole 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 anastrozole 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 anastrozole 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 anastrozole 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 anastrozole; setting; total number of patients; number of patients who received anastrozole; patient population; indication for use of anastrozole; dosage form and strength; dose; ROA; frequency and duration of therapy; use of anastrozole in a combination product; use and formulation of anastrozole in a compounded product; use of anastrozole 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 anastrozole was used in a clinical setting. The systematic literature review and indication from the nominations was reviewed to identify the following medical specialties that would potentially use anastrozole: endocrinology, obstetrics and gynecology, and oncology. 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.

Surveys

A survey was distributed to the members of professional medical associations to determine the use of anastrozole 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 persons. 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

- Anastrozole is not available as an FDA-approved product in the nominated dosage form and ROA.
- Anastrozole is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for anastrozole.
- Anastrozole is not available in the nominated dosage form and ROA in any of the national medical registries searched but it is available in other dosage forms.

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 211 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 177 titles and abstracts were screened. After screening, the full text of 10 articles was reviewed. Finally, 5 studies were included. Five studies were excluded for the following reasons: wrong study design (3 studies); wrong dosage form or ROA (1); duplicate study (1).

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

Characteristics of included studies

The 5 included studies were published between 2013 and 2019. There were 0 experimental studies, 5 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 5 studies were conducted in the US.

A total of 1819 patients participated in the 5 included studies. The number of patients in each study ranged from 1 to 1388.

Outcome measures differed among the studies and included: reduction of tumor volume, improvement in hormonal symptoms, reduced incidence of breast cancer, and estradiol and testosterone levels.

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

Use of anastrozole

One thousand two hundred sixty-eight patients received either anastrozole in combination with testosterone or testosterone alone for hormone deficiency symptoms, administered subcutaneously at a dose of 4-8 mg for 0.28-7.36 years.[18] Seventy-two patients received anastrozole in combination with testosterone for relief of hormone deficiency/menopausal symptoms, administered subcutaneously, no dose was provided.[28] Fourteen patients received anastrozole for treatment of low testosterone due to pituitary-dependent hypogonadism, administered via an unknown route and at an unknown dose.[29] Three hundred forty-four patients received anastrozole in combination with testosterone to prevent elevated estradiol levels and side effects of excess estrogen associated with testosterone therapy, administered subcutaneously at a dose of 16 mg for 0.17-11.6 years.[30] One patient received anastrozole in combination with testosterone for treatment of breast cancer, administered as intramammary implants at a dose of 12 mg with a plan to continue this therapy for a minimum of 1 year.[31]

Refer to Table 6 for summary of dosage by indication.

Anastrozole was used as a compounded product and as a combination product (refer to Tables 8-9).

In 5 studies, the authors' conclusion stated that use of anastrozole was well tolerated and effective. Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 5 included studies, several studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of anastrozole.

Anastrozole is a selective, nonsteroidal aromatase inhibitor (AI). Aromatase, a cytochrome P450 enzyme, catalyzes the conversion of C_{19} androgens (androstenedione and testosterone) to C_{18} estrogens (estrone and estradiol).[32] In premenopausal women, high levels of aromatase are found in the ovaries and placenta, which are the major sites of estrogen production.[32,33] Aromatase is also found in peripheral tissues, including adipose, brain, liver, muscle and breast, which are the major sites of estrogen production in postmenopausal women and men. In the peripheral tissues, aromatase catalyzes the aromatization of circulating androgens, mainly androstenedione made by the adrenal glands, to estrogens.[32-34] Anastrozole blocks the action of aromatase by binding to the enzyme's active site, thereby blocking the conversion of androgens to estrogens in peripheral tissues.[32] Anastrozole has little to no effect on glucocorticoid or mineralocorticoid production in the adrenal glands.[34]

Anastrozole is currently available in the US as an oral 1 mg tablet. The FDA approved this oral form in 1995 for use in postmenopausal women with hormone receptor-positive breast cancer. This remains the primary indication for which anastrozole is used. The 2016 American Society of Clinical Oncology (ASCO) guideline on endocrine therapy for hormone receptor-positive breast cancer stated that "Sequential hormone therapy is the preferential treatment for most women with HR [hormone receptor]-positive MBC [metastatic breast cancer]."[35] The authors of this guideline advised that patients whose tumors express any level of hormone receptors should be offered hormone therapy, including AIs. Hormone receptor-positive breast cancer is the most common subset of early and late-stage breast cancer, with more than 70% of tumors expressing these receptors.[35] The ASCO guideline recommended AIs as the preferred first-line endocrine therapy, administered either alone or with palbociclib or fulvestrant, in postmenopausal women with hormone receptor-positive breast cancer.

For premenopausal women, the guideline recommended ovarian suppression or ablation and tamoxifen or an AI, administered alone or in combination with palbociclib or fulvestrant.

Recently, positive outcomes from a large randomized controlled trial prompted the ASCO to update its guideline on the use of endocrine therapy for breast cancer risk reduction. The International Breast Cancer Intervention Study-II (IBIS-II) evaluated the use of anastrozole for breast cancer prevention in postmenopausal women at high risk for developing this cancer.[12,13] Participants received either oral anastrozole 1 mg daily (1920 participants) or placebo (1944 participants) for 5 years. The median follow-up was 131 months; 250 breast cancers were reported over the study period, 85 in the anastrozole group (4.4% of participants in this group) and 165 in the placebo group (8.5%). This corresponded to a highly significant 49% reduction in all breast cancers for the anastrozole group. There was a 61% decrease in incidence in the first 5 years and 37% decrease in incidence in subsequent years. These findings led the ASCO to recommend that anastrozole (1 mg/day orally for 5 years) be discussed with patients as an alternative to tamoxifen, raloxifene or exemestane for breast cancer risk reduction in postmenopausal women at increased risk of developing breast cancer (strength of recommendation: strong; evidence quality: high).[36] The ASCO guideline advised clinicians to evaluate fracture risk and measure bone mineral density prior to starting AI therapy due to reported increased rate of bone loss in women receiving AIs. Anastrozole, exemestane and raloxifene were not recommended for breast cancer risk reduction in premenopausal women. In the UK, the National Institute for Health and Care Excellence also recommended the use of anastrozole for breast cancer prevention in postmenopausal women at high risk for developing this cancer.[13]

IBIS-II also compelled the US Preventive Services Task Force to update their evidence report on medication use for risk reduction of primary breast cancer in women.[37] The authors of the 2019 evidence report concluded that "Tamoxifen, raloxifene, and aromatase inhibitors were associated with lower risk of primary invasive breast cancer but were also associated with adverse effects that differed between medications."[37] The strength of evidence was considered high for the use of anastrozole versus placebo to reduce the risk of breast cancer, based on the results from the IBIS-II trial. None of the studies included from the systematic literature review evaluated the persistence of the effect of anastrozole after discontinuation of use. The authors noted that although the IBIS-II trial reported no effect of group on major adverse events including fractures, myocardial infarction, deep vein thrombosis, pulmonary embolism, transient ischemic attack or stroke, lack of long-term follow-up data made it impossible to determine whether harms (fractures and cardiovascular events) identified in treatment trials with anastrozole applied to use of anastrozole for risk reduction.[13,37]

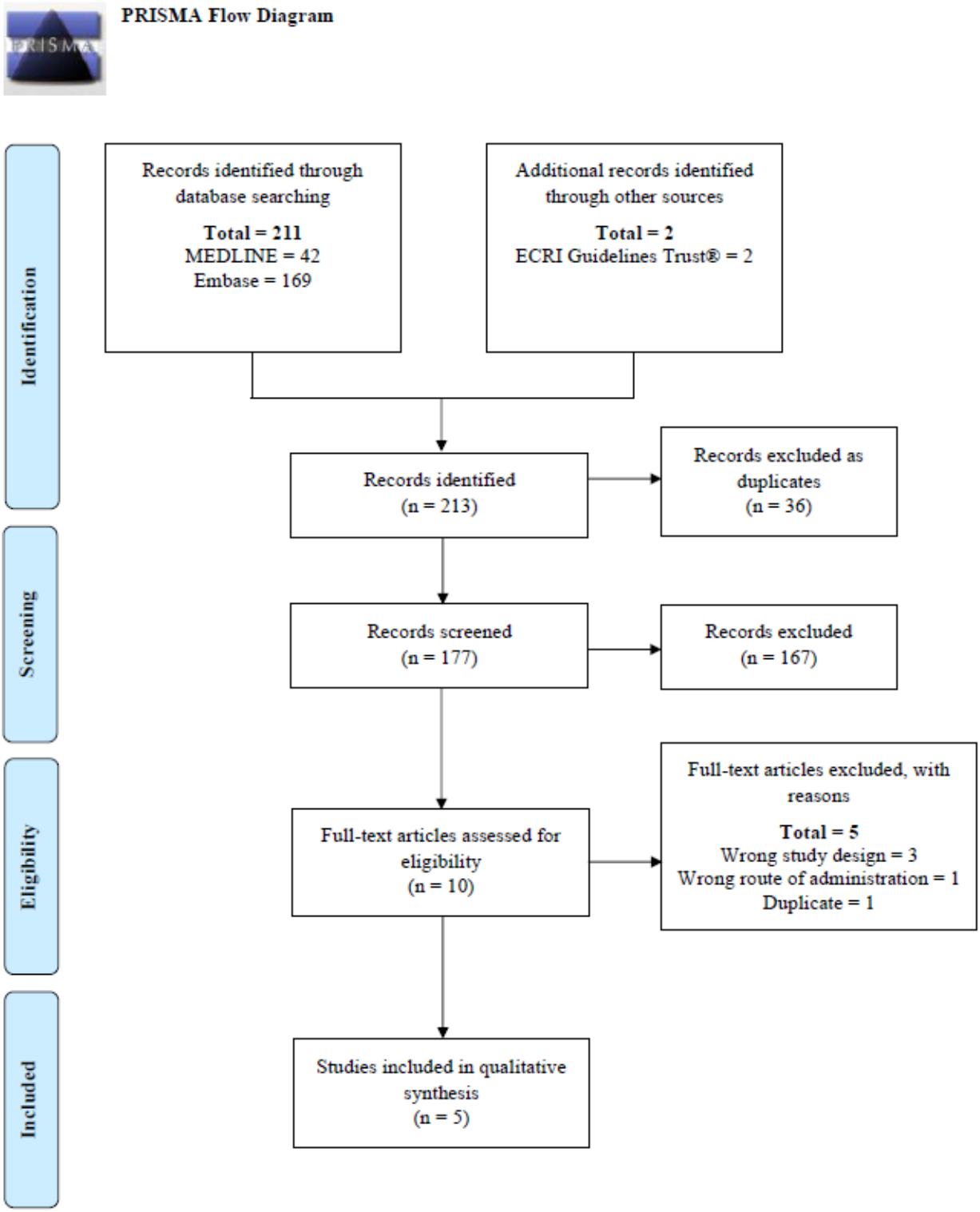
In addition to its established use in women with breast cancer, anastrozole has also been investigated for use in male breast cancer patients. A retrospective study reviewed male breast cancer patients with metastatic disease who had received at least 1 month of treatment with a nonsteroidal (anastrozole or letrozole) or steroidal (exemestane) AI.[16] Five of the 15 patients included in this study received anastrozole. One of these 5 patients had a partial response to anastrozole treatment, 1 had stable disease, and 3 had progressive disease. Estradiol levels were measured in 3 patients who received anastrozole, remaining detectable in 2 of these patients. Overall, the authors concluded AIs were active in male breast cancer patients, but further studies were needed to explore the mechanisms of resistance to AI therapy in these patients.

Anastrozole has also been evaluated for use in patients with gynecological cancers. The PARAGON trial, a single-arm, multicenter phase 2 clinical trial, explored the use of oral anastrozole (1 mg/day) in postmenopausal women with hormone receptor-positive gynecological cancers, including ovarian cancer, peritoneal cancer, endometrial cancer, and granulosa cell tumors. Results reported thus far

have shown a clinical benefit of anastrozole treatment in women with endometrial and ovarian cancers.[38-41] The authors of one article on the PARAGON trial observed that the challenge in the use of AIs in patients with these cancers will be to identify the subset of patients who are most likely to benefit from treatment with an AI.[39]

Anastrozole has also been used in women with endometriosis[26,42,43] and children with short stature.[32,44,45]

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[18,28-31]	5
Experimental	0

Table 4. Number of studies by country

Country	**Number of Studies**
United States (US)[18,28-31]	5
	Total US: 5 Total Non-US Countries: 0

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age range)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Glaser *et al.*, 2014, US[31]	–	1 Patient (0%, 90 y)	• Anastrozole + testosterone • Tamoxifen	Reduction of tumor volume	T + A therapy was well tolerated and effective in treating androgen receptor-positive breast cancer. There was a rapid clinical response to therapy.
Glaser *et al.*, 2013, US[18]	Prospective, observational study	1388 Patients (0%, control age at analysis: 57.8 y ± 9.3, ITT age at analysis: 56.6 y ± 8.9)	• Anastrozole + testosterone or testosterone alone (1268) • Control[b] (119)	Treatment of hormonal symptoms in pre- and post-menopausal women, reduced incidence of breast cancer	"Continuous T and T + A, delivered as a subcutaneous implant, seems to represent safe and effective therapy in treating hormonal symptoms in both pre and postmenopausal women. In this study, safety is verified by the significant decline in breast cancer incidence. We demonstrated that subcutaneous T, and subsequently, T + A, has a protective effect in the breast, and prevented cancer occurrence in some cases."
Glaser *et al.*, 2019, US[30]	Cohort study	344 Patients treated with subcutaneous testosterone, or testosterone combined with anastrozole to prevent elevated estradiol levels (100%, age at evaluation 27.7-84.7 y)	• Anastrozole + testosterone (344)	Estradiol and testosterone levels	Subcutaneous T + A allowed for higher dosing of testosterone and less frequent intervals of insertion; low-dose anastrozole maintained low estradiol levels throughout the implant cycle and prevented side effects attributed to excess estrogen.
Glaser *et al.*, 2014, US[28]	Prospective	72 Breast cancer survivors (0%, not provided)	• Anastrozole + testosterone (72)	Improvement in psychological, somatic, and urogenital symptoms as indicated by a survey response; testosterone levels	T + A implant was effective in relieving hormone deficiency symptoms in breast cancer survivors.

Larocque *et al.*, 2014, US[29]	–	14 Patients with pituitary-dependent hypogonadism due to obesity or type 2 diabetes (100%, not provided)	• Anastrozole (14)	Total free testosterone and estrogen (testosterone to estrogen ratio)	Clinical improvement in all patients in terms of libido or energy; clinically significant rises in testosterone, testosterone to estrogen ratio, and symptomatic improvement indicate anastrozole could be an alternate treatment to testosterone replacement in obese and diabetic men.

Abbreviations: "–", not mentioned; A, anastrozole; ITT, intention-to-treat; T, testosterone.
[a]As defined by authors.
[b]Predetermined that patients receiving only 1 pellet implant (i.e. 3-month therapy) not eligible for analysis, followed as control group.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Breast cancer[31]	12 mg	4 mg	Pellet	Intramammary	13 weeks
Hormone replacement[18,28,29]	4-8 mg	–	Pellet	Subcutaneous	3 months – 3.1 years
Prevent elevated estradiol[30]	16 mg	Anastrozole 8 mg / Testosterone 120 mg	Pellet	Subcutaneous	0.17 – 11.6 years

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No studies from non-US countries included

Table 8. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Anastrozole 4 mg / Testosterone – Subcutaneous/subdermal pellet[18,28,31]	3
Others found in literature	Anastrozole 8 mg / Testosterone 120 mg – Subcutaneous pellet[30]	1

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Prevent elevated estradiol[30]	2019	Compounded with testosterone in a ratio of 15:1:1 (testosterone:anastrozole:stearic acid) into 3.1 or 4.5 mm cylinders; 60 or 120 mg of testosterone and 4 or 8 mg of anastrozole	Pellet	4-8 mg

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. Nine SMEs discussed anastrozole. Amongst these 9 SMEs, there were 6 medical doctors, 1 regulatory affairs specialist, and 2 nurse practitioners. The SMEs specialized and/or were board-certified in gynecology, naturopathy, oncology/hematology, primary care/family medicine, sexual/reproductive medicine, surgery, and urology, working in academic medical practice, hospital, pharmacy/pharma company, and private practice/clinic. The SMEs had been in practice for 9 to 39 years.

Testosterone is one of the most abundant bioactive hormones in men and women with a large impact on overall health, wellness, and well-being. Testosterone is also the major substrate for estradiol and is converted to estradiol via an aromatase enzyme. However, according to one SME, testosterone levels have been decreasing and are around 60-70% lower than they were 50 years. The SME attributed this decline environmental toxins, like phthalates, that affect the estrogenic pathway leading to decreased testosterone levels and an up regulation of aromatase, which is the enzyme that converts testosterone to estradiol, leading to abnormally high levels of estradiol production. Due to the decreasing levels of testosterone, more patients are requiring testosterone replacement but with an up regulation of aromatase this leads to higher levels of estradiol.

Elevated estradiol levels can lead to blood clotting, fat and water retention, and can stimulate breast growth increasing the risk of breast cancer. Estradiol can also lead to irritability and aggression, behaviors that are often attributed to testosterone but are actually a result of elevated estradiol. When replacing testosterone, it is important to estimate how much testosterone is getting converted into estradiol because, according to one SME "you don't want to fix one hormonal problem…and create a secondary problem." The SME continued that "we need to be able to make a balance, so you have enough estradiol to perform all cellular functions without an overproduction of estradiol that creates side effects." Anastrozole is an aromatase inhibitor that plays an important role in in this balance by preventing the conversion of testosterone to estradiol and is considered the "go-to" drug.

In order to allow the balance of testosterone and estradiol, two SMEs stated that they add anastrozole to the testosterone pellets. One SME stated that they add anastrozole to at least 60% of testosterone pellets for their male patients with low testosterone and all their premenopausal patients due to low testosterone and cyclical surges due to ovulation. Another SME adds it to about 95% of their male patients and 80% of their premenopausal patients. Postmenopausal women also may need anastrozole added to the testosterone pellets. Symptoms of low testosterone are in part because they are not ovulating. The ovaries are still responsible for producing testosterone, but they do not produce enough, or the patient may "over-aromatize" and produce too much estrogen. Even patients with low testosterone may have elevated estradiol levels (between 30-60 pg/mL when normal levels are 10-30 pg/mL). One SME said approximately 20% of their postmenopausal patients are on the combination pellet. A 3rd SME uses anastrozole, but as the oral tablet, in men stating that the oral version is widely available and cheap; this SME did not see a need for a pellet.

Due to the risk of estradiol increasing the risk of breast cancer, hormone replacement therapy can be challenging in patients with breast cancer. Approximately 85% of breast cancers are estrogen receptor positive. Testosterone alone cannot be used in these patients because you can stimulate the breast cancer. One SME said that the combination pellet has been effective in the treatment of over 200 breast cancer survivors and they "see almost zero recurrence" in patients who were treated for breast cancer; "I have case after case of tumors responding to this." The SME starts all hormone receptor-positive breast cancer patients on the combination pellet, often at dosages of 8-20 mg pellets, but that number decreases "the

further they get from surgery." While some breast cancer patients may stay on anastrozole for life, the SME noted "once they are 5 years out with low aggressive disease, they might do testosterone alone." The SME said, "the combination implant is necessary," citing a case in which a female patient who refused surgery for a mass has been tumor-free for a year after taking the testosterone/anastrozole combination therapy. Two SMEs also stated that they use anastrozole for breast cancer, however they prescribe the oral tablet and did not see a need for a pellet version since these patients do not typically have swallowing or digestive issues.

One SME believes that testosterone pellets are the most effective way to treat low testosterone because it allows for a physiologic steady-state availability. The SME stated that there are injectable versions of testosterone, but this will lead to a drastic rise in testosterone, then a spike in estrogen, followed by a rapid decline in testosterone. The SME stated that "this is a common but very poor way of trying to replace a hormonal deficiency." Nebido® (testosterone undecanoate), which was recently approved for intramuscular injection, is considered "the best of the non-pellet solutions" according to one SME. This form lasts 2 months, but "causes a lot of muscle pain and can cause muscle rupture." Injections cause hormone levels to spike and fall, creating different side effects throughout the cycle. Creams and gels were found to get men into a therapeutic range of the hormones only 21% of the time. The sublingual product is "like an injection that lasts 4 hours." It makes patients feel better in the short-term, but then the body overproduces estradiol in response, which can make the patient irritable

There are commercially available testosterone pellets and oral anastrozole. However, one SME stated that the testosterone pellets have significantly increased in cost and contain stearic acid, and povidone which can lead to allergies. The oral anastrozole must be taken daily, and due to passage through the portal system, can cause liver irritation and is greatly affected by first pass metabolism, with very little entering circulation. By putting anastrozole into a pellet, patients can be given 3 months' worth of the drug, it does not go through the portal system, so it is more efficient and safer. Adding anastrozole to the pellet also removes any patient compliance issues that may arise with daily oral medication, which is especially important for women with breast cancer. One SME said, "I think they [compounded products] are superior." Compounding testosterone/anastrozole pellets allows for "simultaneous delivery" of both hormones which avoids a "testosterone peak," with few side effects. The compounded pellets are made with cholesterol which reduces the risk of an allergic reaction. One SME stated "the 503B pellets are dramatically better…there is never a reaction, they are very safe."

The pellets are placed in-office into fatty tissue, like the outer buttock for women and "deep in the love handle" for men. The pellets are given every 3 months for women and every 4 months for men; this may vary depending on an individual's physical activity level. The less active a person is, the longer the reserve will last. One SME prescribes pellets in a 15:1 testosterone to anastrozole ratio. Of the 2 SMEs that use pellets, none use anastrozole as a single-agent pellet.

Three SMEs do not prescribe anastrozole. One stated that they are wary of hormones due to the increased risk of malignancy and another does not recommend pellets because they have seen patients with extremely high levels that become symptomatic. One SME said that they refer patients to an oncologist or urologist if hormone therapy is needed.

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, 2 (2%) used compounded anastrozole as a solo product, while 3 (3%) used anastrozole in combination with testosterone. Solo product respondents used compounded anastrozole as a subcutaneous or subdermal pellet (2, 100% of respondents) for hormone replacement (1, 50%) and "none of the above" (1, 50%). Anastrozole / testosterone combination respondents also used anastrozole as a subcutaneous or subdermal pellet (3, 100%), with respondents using it for hormone replacement (2, 67%) and "none of the above (1, 33%) (refer to Table 12).

Solo product respondents used the compounded product due to a lack of commercial products in an appropriate dosage form, strength, or combination (1, 50%) and unidentified other reasons (1, 50%). Anastrozole / testosterone combination respondents used the compounded combination product due to a lack of commercial products in an appropriate dosage form, strength, or combination (2, 50%), lack of commercially available products containing anastrozole / testosterone (1, 25%), and other reasons (1, 25%) (refer to Table 13). The explanation for using compounded anastrozole / testosterone due to lack of appropriate dosage form, strength, or combination was "no pellets are available." The explanation for using compounded anastrozole / testosterone for other reason was "pt preference."

The majority of respondents who used compounded anastrozole as a solo product (2, 100%) did stock non-patient-specific compounded anastrozole at their practice. Similarly, the major majority of respondents who used compounded anastrozole / testosterone as a combination product (2, 67%) did stock non-patient-specific compounded anastrozole / testosterone at their practice, while the other (1, 33%) was not sure if it was stocked. Respondents that did stock non-patient-specific anastrozole as a solo product compounded the products themselves at their practice (2, 100% of respondents); respondents stocking the anastrozole / testosterone combination product purchased, or had a patient purchase, from a compounding pharmacy (2, 100%); while one of the combination product respondents declined to answer this question (refer to Table 14 for how respondents obtained compounded anastrozole).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=96)[a]
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 terminal clinical degree and/or practice setting.
[b]Responses to other: retired from research; Graduate Education Program faculty; "recently moved to FL."

Table 12. Conditions for which anastrozole prescribed or administered

Condition	Responses, n (N=5)[a]
Hormone replacement	3
Other	0
None of the above	2

[a]Out of 96 respondents, 2 reported prescribing or using compounded anastrozole as a solo product; 3 reported prescribing or using compounded anastrozole / testosterone as a combination product.

Table 13. Reasons for using compounded anastrozole

Reason	Responses, n (N=5)[a]
Commercial product not available in desired dosage form, strength or combination	3
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	0
No commercial products	1
Other – patient preference	1

[a]Out of 96 respondents, 2 reported prescribing or using compounded anastrozole as a solo product; 3 reported prescribing or using compounded anastrozole / testosterone as a combination product.

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

Do you stock non-patient-specific compounded anastrozole at your practice?	**Responses, n (N=5)[a]**
Yes	4
No	0
Not sure	1
How do you obtain your stock of non-patient-specific compounded anastrozole?	
Compound yourself at practice	2
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	2
Purchase from outsourcing facility	0
Other	0
No response	1

[a]Out of 96 respondents, 2 reported prescribing or using compounded anastrozole as a solo product; 3 reported prescribing or using compounded anastrozole / testosterone as a combination product.

CONCLUSION

Anastrozole was nominated for hormone replacement, to prevent the conversion of excess testosterone into estrogen/estradiol in female patients with a history of breast cancer and men treated with testosterone replacement therapy, via a 4 mg and 8 mg subcutaneous and subdermal pellet, alone or in combination with testosterone. Anastrozole is not approved in the nominated dosage form and ROA in any of the national medicine registers that were searched. Anastrozole is available in the US as an FDA-approved oral tablet.

In the 5 studies included from the literature review, anastrozole was administered either alone or in combination with testosterone as a subcutaneous or intramammary pellet for treatment of hormone deficiency symptoms, low testosterone due to pituitary-dependent hypogonadism, breast cancer, and prevention of elevated estradiol and side effects of excess estrogen associated with testosterone therapy. The authors of all studies concluded that anastrozole, either alone or in combination with testosterone, was effective. The literature review revealed that oral anastrozole is an established treatment for postmenopausal women with hormone receptor-positive breast cancer and has recently been shown to reduce the risk of breast cancer in postmenopausal women at increased risk for developing this type of cancer. Oral anastrozole has also been used in male breast cancer patients, and women with gynecological cancers or endometriosis.

Amongst the 9 SMEs interviewed, 2 used a testosterone/anastrozole combination pellet with patients, 4 SMEs used the oral form of anastrozole, and 3 did not use anastrozole. SMEs used anastrozole for hormone replacement, to control estrogen levels, and as part of maintenance therapy for hormone receptor-positive breast cancer patients. Anastrozole was used to successfully balance hormone levels in both female and male patients, reducing the side effects of excess estrogen.

From the NPWH survey responses, 2 out of 96 respondents used compounded anastrozole as a solo product, while 3 out of 96 respondents used compounded anastrozole / testosterone in combination. The most common indication respondents used compounded anastrozole products for was hormone replacement. Lack of commercial products in an appropriate dosage form, strength or combination, and patient preference were some of the reasons for using the compounded anastrozole products over an FDA-approved product. Four of the 5 respondents reported stocking compounded anastrozole products at their practice.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 6, 2020
- Date last searched: March 9, 2020
- Limits: Humans (search hedge); English language
- Number of results: 42
- Notes: Included investigational drug numbers due to small number of results

1	anastrozole/	1389
2	anastr#zol$.tw.	1846
3	ici d 1033.tw.	0
4	icid1033.tw.	0
5	zd 1033.tw.	2
6	zd1033.tw.	6
7	or/1-6	2228
8	injections, subcutaneous/	32433
9	injections, intradermal/	6275
10	drug implants/	9097
11	implant$.tw.	391528
12	subcutaneous$.tw.	162832
13	subdermal$.tw.	2371
14	pellet$.tw.	28143
15	or/8-14	584461
16	exp breast neoplasms/	287126
17	exp antineoplastic protocols/	137861
18	chemotherapy, adjuvant/	39875
19	consolidation chemotherapy/	519

20	exp hormone replacement therapy/	24587
21	induction chemotherapy/	2567
22	maintenance chemotherapy/	1591
23	chemoprevention/	5882
24	testosterone/	68702
25	dt.fs.	2184738
26	ad.fs.	1393722
27	tu.fs.	2191668
28	pc.fs.	1264415
29	(breast adj2 (cancer$ or carcinoma$ or malignan$ or neoplas$ or tumo?r$)).tw.	297114
30	chemotherap$.tw.	396197
31	therap$.tw.	2704689
32	treat$.tw.	5356136
33	prevent$.tw.	1379508
34	prophyla$.tw	161148
35	chemoprevent$.tw.	20484
36	chemoprophyla$.tw	6248
37	testosteron$.tw.	80074
38	or/16-37	9668349
39	and/7,15,38	67
40	exp animals/ not humans/	4675662
41	40 not 41	48
42	limit 41to english language	42

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 9, 2020
- Limits: Humans (search hedge); English language
- Number of results: 169
- Notes: Included investigational drug numbers due to small number of results

1	anastrozole'/exp	9478
2	anastrozol*':ti,ab	2996
3	anastrazol*':ti,ab	315
4	ici d 1033':ti,ab,tn	0
5	icid1033':ti,ab,tn	0
6	zd 1033':ti,ab,tn	27
7	zd1033':ti,ab,tn	7
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	9698
9	intradermal drug administration'/de	13308
10	subcutaneous drug administration'/de	100774
11	injection'/de	215204
12	drug implant'/de	4007
13	implant*':ti,ab	549991
14	subcutaneous*':ti,ab	245757
15	subdermal*':ti,ab	3274
16	pellet*':ti,ab	38901
17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	1078420
18	breast tumor'/exp	550573
19	cancer adjuvant therapy'/exp	114274
20	chemotherapy'/exp	655380
21	cancer hormone therapy'/de	20946
22	hormone substitution'/exp	59455

23	androgen therapy'/de	6580
24	chemoprophylaxis'/de	25187
25	testosterone'/de	121174
26	drug therapy':lnk	3843836
27	drug dose':lnk	621819
28	drug administration':lnk	1718631
29	prevention':lnk	1159849
30	(breast NEAR/2 (cancer* OR carcinoma* OR malignan* OR neoplas* OR tumor* OR tumour*)):ti,ab	430815
31	chemotherap*':ti,ab	634554
32	therap*':ti,ab	4074510
33	treat*':ti,ab	7768530
34	prevent*':ti,ab	1877329
35	prophyla*':ti,ab	257449
36	chemoprevent*':ti,ab	26400
37	chemoprophyla*':ti,ab	8323
38	testosterone*':ti,ab	107502
39	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	13269653
40	#8 AND #17 AND #39	216
41	[animals]/lim NOT [humans]/lim	6001338
42	#40 NOT #41	180
43	#40 NOT #41 AND [english]/lim	169

Appendix 2.1. Survey instrument for professional medical associations

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

   - o Yes
   - o No

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

   - o Subcutaneous/subdermal pellet
   - o None of the above

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

   - o Hormone replacement
   - o Other (please explain) _____

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

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

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

7. I obtain compounded anastrozole 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,

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. 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 Anastrozole
   - o Anastrozole as a solo product
   - o Anastrozole/Testosterone 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 anastrozole 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 anastrozole 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 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) _____

17. 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

18. 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) _____
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 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.