Summary Report

Growth hormone-releasing peptide-6

Prepared for:

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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
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GHRP2	Growth hormone-releasing peptide-2
GHRP6	Growth hormone-releasing peptide-6
IGF-1	Insulin-like growth factor-1
ITT	Insulin Tolerance Test
IRB	Institutional Review Board
IV	Intravenous
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 growth hormone-releasing peptide-6 (GHRP6; UNII code: 4H7N4I6X6A), 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 GHRP6 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 GHRP6 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 GHRP6 and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

GHRP6 was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA). GHRP6 was nominated for combination with growth hormone-releasing peptide-2 (GHRP2) and sermorelin acetate (refer to Table 8).

GHRP6 was nominated for growth hormone deficiency (including adult onset), wasting syndrome, and anorexia nervosa via a 0.5-5 mg/mL injection.

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

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

- There is no FDA-approved product that includes GHRP6.
- 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.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of GHRP6 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 GHRP6; name variations of GHRP6 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 GHRP6. 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 two concepts: GHRP6, and injectable administration or therapeutic use (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 December 2, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 13, 2020, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on November 13, 2019 for clinical practice guidelines that recommended the use of GHRP6 and provided sufficient dosing and administration instructions.

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

Study selection

Studies in which GHRP6 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 GHRP6 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 GHRP6 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 GHRP6; setting; total number of patients; number of patients who received GHRP6; patient population; indication for use of GHRP6; dosage form and strength; dose; ROA; frequency and duration of therapy; use of GHRP6 in a combination product; use and formulation of GHRP6 in a compounded product; use of GHRP6 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 GHRP6 was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use GHRP6: endocrinology, naturopathy, pediatrics and neonatology, and primary care and internal medicine. 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 GHRP6 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

- GHRP6 is not available as an FDA-approved product.
- GHRP6 is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for GHRP6.
- GHRP6 is not available in any of the foreign registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 457 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 345 titles and abstracts were screened. After screening, the full text of 29 articles was reviewed. Finally, 0 studies were included. Twenty-nine studies were excluded for the following reasons: wrong study design (14 studies); wrong dosage form or ROA (5); wrong indication (4); wrong substance (2); GHRP6 used as brand or proprietary product (2); GHRP6 not used clinically (1); language other than English (1).

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

Characteristics of included studies

No studies were included.

Use of GHRP6

No studies were included.

Pharmacology and historical use

Several studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of GHRP6.

Growth hormone (GH), also known as somatotropin, is a protein that is produced by the somatotroph cells found in the anterior lobe of the pituitary gland. GH receptors are found throughout the body and are responsible for many metabolic functions including promoting growth in children, increasing lipolysis, stimulating protein synthesis, and antagonizing insulin.[8] GH is regulated by 3 hypothalamic hormones: growth hormone releasing hormone (GHRH), somatostatin, and ghrelin.[9] GHRH and ghrelin stimulate GH release while somatostatin inhibits release.[9] GH has a pulsatile secretion with

production occurring primarily at night and pulses following exercise, trauma, and sleep.[8] GH production rises in childhood with the peak occurring at puberty and then declining with age. As GH declines with age, exogenous administration has many proposed benefits including increasing lean muscle mass, decreasing fat mass, increasing exercise tolerance, and increasing muscle strength.[8] However, due to potential safety concerns associated with supratherapeutic GH levels resulting from the bypass of the normal, regulatory feedback, there has been an interest in the use of GH secretagogues.[6,8]

GH secretagogues include GH-releasing peptides (GHRPs), like GHRP2 and GHRP6, and GHRH analogs, like sermorelin. GH secretagogues stimulate the endogenous secretion of GH, GHRPs increase the number of somatotrophs releasing GH and GHRH analogs increase the amount of GH secreted, which maintains levels within normal physiologic levels.[8,10] The action of GHRPs is independent of GHRH so as a result, when a GHRH analog and a GHRP are used together they have a synergistic effect stimulating the release of GH.[6,8]

GHRPs were first synthesized in 1977 and GHRP6 was the first that was found to have significant in vivo activity; however, it must be administered frequently and as an injection due to its poor oral bioavailability and short half-life.[8] Additional research was conducted to identify subsequent molecules with a more favorable bioavailability and half-life resulting in the synthesis of numerous GH secretagogues.[6] Based on the structure of GHRP6, new GH secretagogues were developed, including GHRP1 and GHRP2.[11] GHRP2 is more potent than GHRP6 with a slightly longer half-life but with a wide oral bioavailability that is still predominantly administered as an injection.[8,10]

In 1989 Ilson et al assessed the serum GH response of GHRP6 by administering GHRP6 to 17 healthy men in doses ranging from 0.05-2.5 mcg/kg intravenous (IV) in 30 mL of saline infused over 30 minutes compared to 8 men who received saline.[12] Two baseline GH levels were measured followed by 3 levels during the infusion and 7 levels up to 24 hours after the infusion. They found that GHRP6 resulted in a dose-dependent GH increase that peaked at 45 minutes and decreased to baseline levels at 210 minutes. This study showed that GHRP6 is able to stimulate the release of GH.[12]

The insulin tolerance test (ITT) is the primary method used to diagnose GH deficiency. However, due to challenges associated with reproducibility, the impact of patient-specific characteristics (e.g. age, amount of adipose tissue), contraindications (e.g. heart disease, seizure disorders), and lack of a normal range, there is an interest in identifying a more convenient diagnostic tool.[13] Due to the ability of GHRH and GHRP6 to elicit an increase in GH levels coupled with the lack of side effects, several studies have evaluated the use of GHRP6 in combination with GHRH as an alternative tool to diagnose GH deficiency.[11,14] Popovic et al studied the combination in 125 patients with organic pituitary disease who had an ITT within the previous year and 125 healthy controls.[13] All participants received GHRH 1 mcg/kg IV and GHRP6 1 mcg/kg IV. Baseline GH levels were drawn twice prior to administration and 6 times post-administration. The study found that "the GHRH / GHRP6 test is a convenient, safe and reliable test for adult GH deficiency and is not confounded by clinical factors known to alter GH secretory patterns."[13] Similarly, Leal et al administered a bolus of GHRH 1 mcg/kg IV followed by GHRP6 1 mcg/kg IV to 146 adult patients with pituitary disease and 203 healthy controls.[15] The authors reached a similar conclusion to Popovic et al stating that the test is a convenient, safe, and reliable method to determine GH reserve.[15]

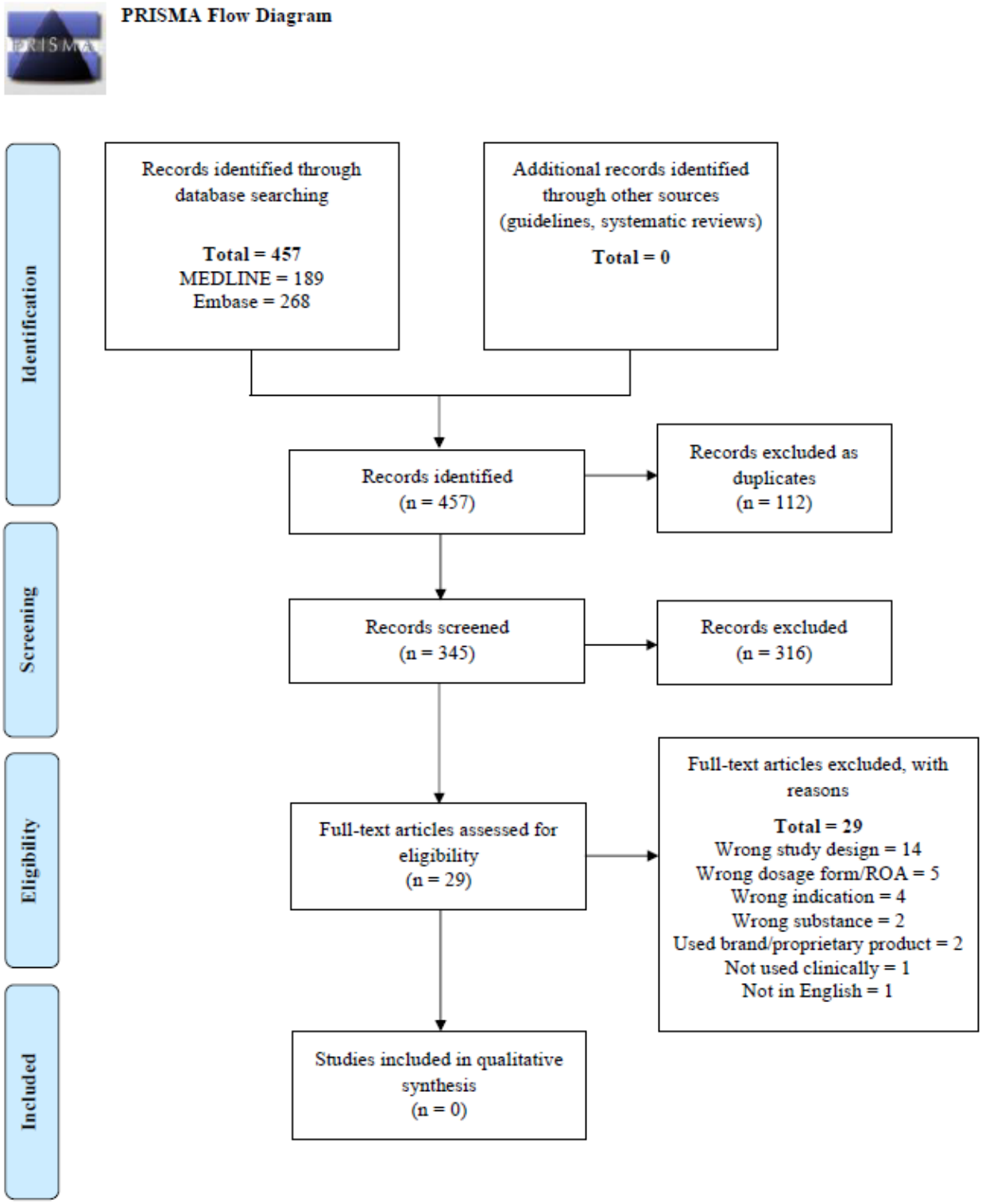
Petersenn et al compared GH release after administration of GHRP6 alone and GHRP6 in combination with GHRH to that of the ITT to diagnose GH deficiency in adults.[16] Twenty adult patients with suspected pituitary or adrenal disease underwent the ITT, followed by GHRP6 1 mcg/kg

IV, and lastly GHRH 1 mcg/kg IV with GHRP6 1 mcg/kg IV. It was found that GHRP6 alone and in combination with GHRH was able to correctly identify all patients with GH deficiency as defined by the ITT. The authors concluded that GHRP6 alone or in combination appears to be as effective as the ITT to diagnose GH deficiency in adults.[16] Lastly, Alaioubi et al compared the ability of GHRP6 to diagnose GH deficiency to the ITT.[17] Forty-nine patients with suspected hypothalamic or pituitary disease underwent the ITT followed by GHRP6 1 mcg/kg IV. These patients were compared to 20 healthy controls who also received GHRP6 1 mcg/kg IV. The authors found that GHRP6 was more potent in releasing GH than hypoglycemia from the ITT, the peak GH level occurred earlier than with the ITT, and there were no side effects observed with GHRP6. They concluded that GHRP6 is an acceptable alternative to the ITT.[17]

Traumatic brain injury (TBI) is also associated with hypopituitarism and subsequently GH deficiency.[18] Due to the prevalence of TBI and the cumbersome and expensive nature of testing there is a need for a cheaper test. A single GH level drawn 30 minutes post administration of GHRH and GHRP6 has been proposed as a possible alternative test.[18] Castro et al studied the ability of the combination to diagnose GH deficiency in patients who had suffered a TBI. Eighty-three adult patients with a history of TBI were administered GHRH 1 mcg/kg IV followed by GHRP6 1 mcg/kg IV. The authors found that the GH peak that occurred within 30 minutes after administration was sufficient to diagnose GH deficiency and concluded that due to the convenience, cost, and rapid results this combination could be used to screen larger populations.[18]

Sigalos et al conducted a retrospective review of 105 hypogonadal men on testosterone therapy who were also prescribed a combination of GHRP2 100 mcg / GHRP6 100 mcg / sermorelin 100 mcg subcutaneously 3 times a day in order to increase lean body mass and fat loss.[6] Of these 105 men, 14 patients met the authors' inclusion criteria regarding adherence to the dosing regimen and baseline insulin-like growth factor 1 (IGF-1) levels less than 200 ng/mL were included in the study.[6] IGF-1 is regulated by GH and due to the short half-life of GH, serves as a surrogate to assess GH levels.[6,8] The authors evaluated the impact of the combination therapy on IGF-1 levels and found that it led to a significant increase in IGF-1 levels.[6] The authors suggested that the combination therapy may be beneficial in wasting conditions where increases in fat-free mass are desirable.[6]

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

No studies included

Table 4. Number of studies by country

No studies included

Table 5. Summary of included studies

No studies included

Table 6. Dosage by indication – US

No studies included

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combinations

	Combination Formula	**Number of Studies**
Nominated	GHRP2 3 mg / GHRP6 3 mg / Sermorelin acetate 3 mg	0

Abbreviations: GHRP2, growth hormone-releasing peptide-2; GHRP6, growth hormone-releasing peptide-6.

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No studies included

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Four SMEs discussed GHRP6. The 4 SMEs were medical doctors. The SMEs specialized and/or were board-certified in endocrinology, naturopathy, and urology, working in academic medical center, private practice/clinic, and retired. The SMEs had been in practice for 8 to 43 years.

GH is commercially available as an FDA approved product, however, it has very narrow indications and is tightly regulated. When GH is administered exogenously as an injection, the natural secretion is inhibited. It was well known that morphine stimulates GH release and in the 1970's there was interest in the synthesis of opiate-like peptides and their potential ability to stimulate the release of GH. This led to the development of GHRP that was shown to "stimulate growth hormone without any analgesic effect and was not addictive." In developing GHRP, researchers discovered that it worked on a secretagogue receptor separate from GHRH, which works on a GHRH receptor. In contrast to GH, when a GH secretagogue is administered it stimulates GH release and "the axis can respond to it" which "restores the growth hormone to what it should be and secreted, and that's really important for normal growth."

GH secretagogues may be used as single agents or in combination and are more often elective "patient demand-based medicine." In many cases people seek these drugs as "lifestyle medications" to improve the appearance of their skin, hair, or body. One SME specializing in urology said that most of their patients come in with a hormone deficiency, which is usually testosterone. The patients are started on hormone replacement therapy and have positive results but still have a desire to improve their physical appearance, which may lead to prescribing GH secretagogues as a solution. In order to determine if a GH secretagogue would be appropriate, some SMEs may look at a patient's IGF-1 level. The IFG-1 level is examined because growth hormones in the body have a half-life of 2-3 minutes, so "it's very difficult to do a growth hormone assay." IFG-1 has a half-life of 16-18 hours, according to one SME, so it provides "a good corollary for growth hormone effects." If a patient starts with a low-normal to low IGF-1 level of less than 150 ng/mL, then they will likely benefit from a GH secretagogue.

One SME noted that GH and GH secretagogues address a more limited set of symptoms to make a patient feel better, look better, or mitigate muscle loss. There have been some studies that have shown that when GH secretagogues are used together they have a synergistic effect. For example, GHRP2 or GHRP6 in combination with sermorelin leads to a "stronger growth hormone response, or growth hormone secretary response." These synergies are the result of "receptor interactions in the growth pathway that will accentuate the response." They amplify the response on the receptor and interact at different receptors, stimulating different methods of releasing growth hormone. By combining hormones which have different molecular effects on the pathways, a synergistic effect can be achieved. A "trending" combination right now is CJC-1295 (a GH secretagogue) and ipamorelin. Ipamorelin inhibits somastatin, a "downstream inhibitor of the growth hormone pathway," which results in "stepping on the gas" and "releasing the brake" to create a synergistic effect. An SME specializing in urology used the combination of GHRP2 / GHRP6 / sermorelin for weight loss and to improve sperm count in morbidly obese men, and for men with hypogonadal symptoms with "low or borderline IGF-1 levels."

There is "limited literature" about the specific dose and/or combination of GHRPs that should be used. Additionally, most of the literature focused on "what's the impact going to be on the growth hormone pathway" and not the downstream effects (i.e., simulate muscle growth, fat loss, other measurable effects). As a result, patients are typically started on a low dose that can then be titrated up as needed. The typical dosing for injectable GHRP is 100-500 mcg/day with up to 1,000 mcg/day with sermorelin. The dosage is gradually increased if they patients do not develop side effects. For both adult and

pediatric patients, GH secretagogues, especially GHRP2 and GHRP6, require multiple doses per day for "optimal effects." The circadian rhythm of the growth hormone pathway involves numerous "peaks and troughs throughout the day." This makes in-office dosing impossible. The secretagogues are administered subcutaneously, which "can be done very easily at home."

There is a "dose response effect" beyond which the body will no longer respond to more medication, which impacts dosing. There are typically few side effects and "it's very hard to overshoot." The feedback mechanism of the secretagogues is intact, making it difficult to "overtreat patients" and offering a safety device to clinicians. To measure outcomes, SMEs may track IGF-1 levels but, "it takes a while for IGF-1 to actually go up." One SME noted that some clinicians will monitor progress by the physical changes a patient experiences since they "prescribe these types of medications for patients who want a desired physical outcome" instead of IGF-1 levels.

Three of the 4 SMEs had used the GH secretagogues GHRP2 and GHRP6. While there is limited literature to base clinical decisions on, "there are informed decisions that are being made" regarding their use. One SME stated that the lack of literature does not mean these drugs should not be used, stating that the drugs are "much safer than growth hormones, because they're stimulating the natural pathway," instead of shutting it down and overriding the natural pathway, like with GH. The SME continued that "anecdotally over the years…they [GH secretagogues] seem to work as advertised, and they seem to be quite safe, but we don't have the peer review literature to prove that, just yet." The SME who did not use growth hormones cited a risk of promoting malignancy, a lack of evidence-based research, and expense.

Results of survey

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

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which GHRP2 / GHRP6 / sermorelin acetate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded GHRP2 / GHRP6 / sermorelin acetate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded GHRP2 / GHRP6 / sermorelin acetate

No respondents to survey distributed via professional medical associations

CONCLUSION

GHRP6 was nominated for inclusion on the 503B Bulks List as an injection to treat growth hormone deficiency (including adult onset), wasting syndrome, and anorexia nervosa. GHRP6 is not available in the nominated dosage form and ROA in any of the national medical registries searched.

Zero studies were included from the literature review. However, several studies that did not meet the inclusion criteria described the use of GHRP6 in the diagnosis of GH deficiency. These studies found that GHRP6, either alone or in combination with GHRH, compared favorably to the ITT for the diagnosis of GH deficiency, including in patients with TBI. One study described the use of the GHRP2 / GHRP6 / sermorelin in hypogonadal men on testosterone therapy. Three SMEs had used GHRP6 and 1 had used the GHRP2 / GHRP6 / sermorelin combination. The SME who used the GHRP2 / GHRP6 / sermorelin combination prescribed it for patients who were obese and/or had hypogonadal symptoms and wanted to lose weight and improve their sperm count. Several SMEs stated that there was limited outcomes-based human research on the clinical use of GH and GH secretagogues, making it difficult to know the ideal combination and dose of medication to use, and the effects of long-term use. One SME stated that this did not mean that GH secretagogues should not be used because they appear quite safe, only that more research on their use is needed.

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

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to November 27, 2019
- Date last searched: December 2, 2019
- Limits: Humans (search hedge); English language
- Number of results: 189
- Notes: Investigational drug numbers included due to small number of results.

1	growth hormone releasing peptide 6.tw.	96
2	GH releasing peptide 6.tw.	78
3	GHRP 6.tw.	555
4	GHRP-6.tw.	34
5	skf 110679.tw.	11
6	skf110679.tw.	0
7	u 75799e.tw.	0
8	u75799e.tw.	0
9	or/1-8	633
10	drug administration routes/	5596
11	exp administration, intravenous/	141170
12	infusions, parenteral/	26196
13	injections/	41905
14	injections, intra-arterial/	9146
15	injections, intramuscular/	30630
16	injections, intravenous/	81375
17	injections, subcutaneous/	32255
18	administration & dosage.fs.	1380015
19	inject$.tw.	720197

20	infusion$.tw.	240321
21	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11900
22	subcutaneous$.tw.	160735
23	intravenous$.tw.	331963
24	intra venous$.tw.	563
25	intravascular$.tw.	46471
26	intra vascular$.tw.	296
27	intramuscular$.tw.	51002
28	intra muscular$.tw.	700
29	drug therapy/	30234
30	hormone replacement therapy/	9780
31	drug effects.fs.	2924596
32	drug therapy.fs.	2159915
33	tu.fs.	2172243
34	therap$.tw.	2651976
35	treat$.tw.	5261497
36	or/10-35	9934888
37	and/9,36	495
38	exp animals/ not humans/	4646734
39	37 not 38	190
40	limit 39 to english language	189

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: December 2, 2019
- Limits: Humans (search hedge); English language
- Number of results: 268
- Notes: Investigational drug numbers included due to small number of results.

1	histidyl dextro tryptophylalanyltryptophyl dextro phenylalanyllysinamide'/de	574
2	growth hormone releasing peptide 6':ti,ab,tn	110
3	gh releasing peptide 6':ti,ab,tn	79
4	ghrp 6':ti,ab,tn	679
5	GHRP-6':ti,ab,tn	49
6	skf 110679':ti,ab,tn	25
7	skf110679':ti,ab,tn	0
8	u 75799e':ti,ab,tn	0
9	u75799e':ti,ab,tn	0
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	910
11	drug administration route'/de	7709
12	parenteral drug administration'/de	2047
13	intramuscular drug administration'/de	71382
14	intravascular drug administration'/de	308
15	intravenous drug administration'/de	391062
16	subcutaneous drug administration'/de	100716
17	drug administration':lnk	1687505
18	inject*':ti,ab	1062540
19	infusion*':ti,ab	346804
20	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	17821
21	subcutaneous*':ti,ab	240061
22	intravenous*':ti,ab	473351

23	intra venous*':ti,ab	1408
24	intravascular*':ti,ab	65819
25	intra vascular*':ti,ab	665
26	intramuscular*':ti,ab	72345
27	intra muscular*':ti,ab	1253
28	drug therapy'/de	681571
29	add on therapy'/de	18175
30	drug comparison'/exp	131448
31	drug dose comparison'/de	37582
32	drug dose escalation'/de	21784
33	drug dose increase'/de	43461
34	drug dose intensification'/de	833
35	drug dose reduction'/de	72128
36	drug dose regimen'/de	34739
37	drug dose sequence'/de	1252
38	drug dose titration'/de	25670
39	drug indication'/de	62158
40	hormonal therapy'/de	44134
41	hormone substitution'/de	36368
42	lack of drug effect'/de	29680
43	loading drug dose'/de	21398
44	low drug dose'/de	130293
45	maintenance drug dose'/de	8389
46	optimal drug dose'/de	8746
47	recommended drug dose'/de	17214
48	single drug dose'/de	81637

49	drug comparison':lnk	588616
50	drug dose':lnk	618769
51	drug therapy':lnk	3774607
52	therap*':ti,ab	3963810
53	treat*':ti,ab	7640923
54	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #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 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53	12717322
55	#10 AND #54	649
56	[animals]/lim NOT [humans]/lim	5957252
57	#55 NOT #56	274
58	#55 NOT #56 AND [english]/lim	268

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded GHRP2 / GHRP6 / sermorelin acetate as a combination product. 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 GHRP2 / GHRP6 / sermorelin acetate as a combination product to your patients?

   - o Yes
   - o No

3. I prescribe or administer GHRP2 / GHRP6 / sermorelin acetate as a combination product for the following conditions or diseases: (check all that apply)

   - o Anorexia nervosa
   - o Growth hormone deficiency
   - o Wasting syndrome
   - o Other (please explain) _____

4. I use compounded GHRP2 / GHRP6 / sermorelin acetate as a combination product 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 GHRP2 / GHRP6 / sermorelin acetate as a combination product.
   - o Other (please explain) _____

5. Do you stock non-patient-specific compounded GHRP2 / GHRP6 / sermorelin acetate as a combination product at your practice?

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

6. I obtain compounded GHRP2 / GHRP6 / sermorelin acetate as a combination product from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

7. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

8. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 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.