Summary Report

# Sermorelin acetate

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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# Frequently Used Abbreviations

| | |
|---|---|
| API | Active Pharmaceutical Ingredient |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration |
| GH | Growth hormone |
| GHD | Growth hormone deficiency |
| GHRH | Growth hormone-releasing hormone |
| GHRP-2 | Growth hormone-releasing peptide-2 |
| GHRP-6 | Growth hormone-releasing peptide-6 |
| IRB | Institutional Review Board |
| IGF-1 | Insulin-like growth factor-1 |
| ITT | Insulin tolerance test |
| 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 sermorelin acetate (UNII codes: 89243S03TE and 00IBG87IQW), 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 sermorelin acetate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how sermorelin acetate has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of sermorelin acetate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

## REVIEW OF NOMINATIONS

Sermorelin acetate was nominated for inclusion on the 503B Bulks List by Olympia Pharmacy and the Outsourcing Facilities Association (OFA). Sermorelin acetate was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Sermorelin acetate was nominated for growth hormone deficiency (GHD) and adult-onset GHD via a 0.5-9 mg/mL injectable product.

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

The reason provided for nomination to the 503B Bulks List is that sermorelin acetate is not currently available in an FDA-approved drug product; it has been discontinued by the manufacturer, but not for reasons of safety or effectiveness.

## METHODOLOGY

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of sermorelin acetate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for sermorelin acetate; name variations of sermorelin acetate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status

and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing sermorelin acetate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

*Systematic literature review*

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: sermorelin acetate; and injectable administration, or diagnostic 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 February 3, 2020. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on October 23, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on October 23, 2019 for clinical practice guidelines that recommended the use of sermorelin acetate and provided sufficient dosing and administration instructions.

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

Study selection

Studies in which sermorelin acetate was used in the nominated dosage form, ROA and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if sermorelin acetate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which sermorelin acetate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of sermorelin acetate; setting; total number of patients; number of patients who received sermorelin acetate; patient population; indication for use of sermorelin acetate; dosage form and strength; dose; ROA; frequency and

duration of therapy; use of sermorelin acetate in a combination product; use and formulation of sermorelin acetate in a compounded product; use of sermorelin acetate compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

*Interviews*

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances sermorelin acetate was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use sermorelin acetate: endocrinology, naturopathy, pediatrics, and urology. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

*Survey*

A survey was distributed to the members of professional medical associations to determine the use of sermorelin acetate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

## CURRENT AND HISTORIC USE

*Results of background information*

- Sermorelin acetate is not available as an FDA-approved product in the nominated dosage form and ROA.
- Sermorelin acetate was available as an FDA-approved injectable product that was discontinued, not for reasons of safety or efficacy.
- Sermorelin acetate is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for sermorelin acetate.
- Sermorelin acetate is not available in any of the national medical registries searched in the nominated form and ROA.

Table 1. Currently approved products – US

*No approved products in the US*

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

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

*Results of literature review*

Study selection

Database searches yielded 619 references; 9 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 466 titles and abstracts were screened. After screening, the full text of 65 articles was reviewed. Finally, 2 studies were included. Sixty-three studies were excluded for the following reasons: sermorelin acetate used as brand or proprietary product (47 studies); wrong study design (13); wrong substance (2); wrong indication (1).

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

Characteristics of included studies

The 2 included studies were published in 1996. There were 2 experimental studies, 0 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 2 studies were conducted in Italy.

A total of 435 patients participated in the 2 included studies. The number of patients in each study ranged from 55 to 380.

The outcome measure for the included studies was peak serum growth hormone (GH) response.

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

## Use of sermorelin acetate

Two hundred seventy-nine patients received sermorelin acetate as an experimental diagnosis tool for GHD, administered intravenously as 1 mcg/kg doses, either once or twice.

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

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

In the 2 included studies, the authors' concluding statement recommended the use of sermorelin acetate for the diagnosis of GHD in adults.[8,9] Refer to Table 5 for summary of authors' conclusions.

## Pharmacology and historical use

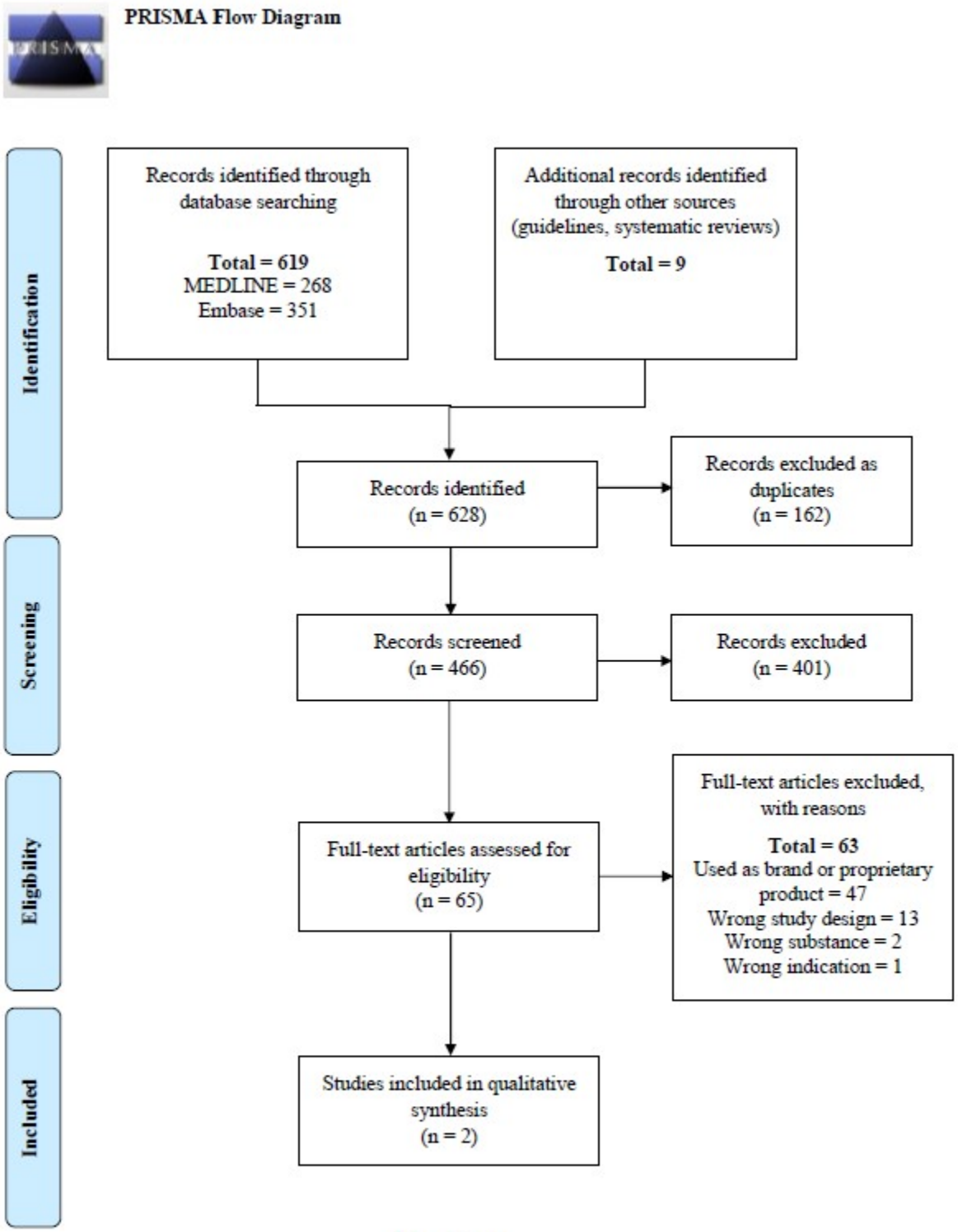
In addition to the 2 included studies, 1 study was identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of sermorelin acetate.

In 2009, a review article commented that the combined growth hormone-releasing hormone (GHRH also known as sermorelin acetate) and arginine (GHRH-ARG) test was considered a more reliable alternative for diagnosing adult GHD, compared to the gold standard insulin tolerance test (ITT).[10] However, this was before July 2008, when the manufacturer, EMD Serono, Inc., decided to indefinitely discontinue the manufacture of Geref® (sermorelin acetate) in the US.[10] According to this review, the use of the GHRH-ARG test comes from the idea "that in healthy normals, GHRH triggers the release of GH from the pituitary somatotroph cells, whereas ARG is believed to potentiate GHRH-stimulated somatotroph secretion via inhibition of hypothalamic somatostatin release."[10] If a patient has pituitary GHD, then the somatotroph cells are less responsive and do not adequately release growth hormone in response to GHRH or ARG.[10]

Yuen mentioned that endocrinologists may lack the capability to conduct ITT in an office setting, as well as concerns about the safety, reproducibility, and specificity of this test.[10] Not only is the ITT described as causing an unpleasant adrenergic response through inducing hypoglycemia, the patient requires "close monitoring by trained medical personnel to ensure that adequate hypoglycemia (blood glucose nadir level <40mg/dl) is achieved without inducing dangerous neuroglycopenia and that correction of the insulin-induced hypoglycemia is appropriately instituted."[10] Coupled with contraindications in patients with severe reactions to hypoglycemia (such as a history of seizure disorder or ischemic heart disease), there are multiple reasons that the ITT may not be the preferred diagnostic for GHD.

Yuen's review also discussed an alternative diagnostic test to either GHRH or the ITT, the glucagon stimulation test (GST). It was described as a relatively inexpensive 4-hour test, and well-tolerated amongst patients, "with the only contraindication being in patients who are malnourished or have not eaten for more than 48 h."[10] He also mentioned the use of other GH secretagogues, such as growth hormone-releasing peptide-2 (GHRP-2), growth hormone-releasing peptide-6 (GHRP-6), alone or in combination as potential diagnostic tests.[10] The limits, however, included lack of availability in the US and "that these agents are more likely to explore the pituitary somatotroph releasable pool and might potentially induce misleadingly normal peak GH responses in hypothalamic GHD."[10]

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




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

Table 3. Types of studies

| **Types of Studies** | **Number of Studies** |
|---|---|
| Descriptive | 0 |
| Observational | 0 |
| Experimental[8,9] | 2 |

Table 4. Number of studies by country

| **Country** | **Number of Studies** |
|---|---|
| Italy[8,9] | 2 |
| | Total US: 0<br>Total Non-US Countries: 2 |

Table 5. Summary of included studies

| Author, Year, Country | Study Type[a] | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|---|---|---|---|
| **Indication: Diagnosis of Growth Hormone Deficiency in Adults** | | | | | |
| Ghigo *et al.*, 1996, Italy[8] | – | 54 Patients with hypopituitarism (44%, range 20-80 y)<br>326 Healthy adults (30%, range 20-80 y) | • IGF-1 (380)<br>• PD + GHRH (127)<br>• ARG + GHRH (113) | Peak serum GH response | IGF-1 and PD + GHRH testing were reliable in young adults, but ARG + GHRH was the most consistent throughout the adult lifespan and seemed the most appropriate for patient compliance and safety. |
| Valetto *et al.*, 1996, Italy[9] | – | 10 Normal children (60%, mean 12 ± 0.9 y)<br>18 Normal young adults (56%, mean 31.1±1.3 y)<br>12 Elderly patients (17%, mean 74.4 ± 1.8 y)<br>15 Patients with panhypopituitarism GHD (60%, mean 40.9 ± 4.1 y) | • ARG + GHRH (55) | Peak serum GH response | The ARG + GHRH has clear normal limits and reproducibility and confirms the hypothesis that it is the first choice to diagnose GH deficiency in adults. |

Abbreviations: "–", not mentioned; ARG, arginine hydrochloride; GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone-releasing hormone; IGF-1 insulin-like growth factor; PD, pyridostigmine.
[a]As defined by authors.

Table 6. Dosage by indication – US

*No studies included*

Table 7. Dosage by indication – non-US countries

| Indication | Dose | Concentration | Dosage Form | Route of Administration | Duration of Treatment |
|---|---|---|---|---|---|
| Diagnosis of growth hormone deficiency in adults[8,9] | 1 mcg/kg | – | – | Intravenous | Once-Twice |

Abbreviations: "–", not mentioned.

Table 8. Number of studies by combination

| | Combination Formula | Number of Studies |
|---|---|---|
| Nominated | Sermorelin acetate 3 mg / GHRP-2 3 mg / GHRP-6 3 mg per vial – injectable | 0 |

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 sermorelin acetate. Amongst these 4 SMEs, there were 3 medical doctors and one pharmacy technician. The SMEs specialized and/or were board-certified in endocrinology, neuroendocrinology, sexual/reproductive health, and urology, working in academic medical center, private practice, and other (retired). The SMEs had been in practice for 8 to 43 years.

Geref® (sermorelin) was developed as a very short-acting GHRH by EMD Serono, Inc. GHRH acts on the GHRH receptor, producing different effects than when the GH secretagogue receptor (also known as the ghrelin receptor) is activated. The SME said that more recently there was a longer-acting preparation with once daily injections, "but when the short acting was available, it stimulated growth, but it wasn't equivalent to super pharmacologic doses of growth hormone."

GHRH was used to diagnose GHD, as well as a treatment for GHD; however, the SME did not think anyone is currently using it for treatment purposes. Another SME said that they use sermorelin in patients with hypogonadal symptoms and low or borderline insulin-like growth factor-1 (IGF-1) levels, as well as to help patients with weight loss or improve sperm counts in very heavy men. A range of doses are used, with most of the injectable agents having doses that range from 100-500 mcg/day, though sermorelin can get as high as 1000 mcg/day. Practitioners track IGF-1 levels and will adjust the dose based off these levels. However, it takes a while for IGF-1 to increase as a result of the injections, and there is a point where the body will no longer respond to increased doses. As a result, "it's very hard to overshoot."

Regarding the combination of sermorelin with GHRP-2 and GHRP-6, an SME said that there is a synergistic effect on the growth hormone pathway. However, there has not been a lot of data beyond cellular or animal studies and small non-outcomes based human studies. As a result, clinicians are less likely to give this combination since they do not know what outcome to expect. An SME also stated that GHRP-2 and GHRP-6, like a majority of secretagogues, require multiple doses per day for optimal effects; sermorelin can be administered as a once daily dose, typically at night when the growth hormone pathway is most active.

When asked if they knew why EMD Serono, Inc. discontinued manufacturing sermorelin acetate, one SME responded that "Serono was also making growth hormone so they didn't want to compete with themselves, I guess." The only gap in the market since sermorelin stopped getting produced was from a testing point of view, though now there is a GH secretagogue, macimorelin (Macrilen®), approved in the US for the diagnosis of adult GHD. Macimorelin is now being studied for use in children. According to one SME, currently the only way to access sermorelin, along with other growth hormone secretagogues, is through a compounding pharmacy. However, another SME said that sermorelin is not being produced by the outsourcing facility anymore because "it is not on the category one list and I don't think it will be any time soon."

*Results of survey*

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

Table 11. Characteristics of survey respondents

*No survey respondents*

Table 12. Conditions for which sermorelin acetate prescribed or administered

*No survey respondents*

Table 13. Reasons for using compounded sermorelin acetate

*No survey respondents*

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

*No survey respondents*

## CONCLUSION

Sermorelin acetate was nominated for inclusion on the 503B Bulks List for GHD and adult-onset GHD via an injectable product. Sermorelin acetate is not approved in any of the national medical registries searched.

From the literature review and interviews, sermorelin acetate was previously available as an FDA-approved product Geref® before being discontinued in 2008 for reasons not related to safety or efficacy. When administered with arginine, sermorelin was considered to be a more reliable alternative for diagnosing adult GHD when compared to the gold standard, the ITT. Besides reliability, concerns about safety may make some practitioners less likely to use the ITT. The idea behind the use of sermorelin is that in normal patients, the introduction of GHRH would stimulate release of GH; in patients with pituitary GHD, the somatotroph cells are less responsive and release less GH. With sermorelin acetate no longer available as an FDA-approved product, compounding and outsourcing facilities are the only ways for practitioners to obtain sermorelin acetate, though since it is not on the category one bulk drugs list, outsourcing facilities are not allowed to compound sermorelin acetate in bulk. Other uses for sermorelin acetate are for patients with hypogonadal symptoms coupled with low or borderline IGF-1 levels, weight loss, or improving sperm counts in very heavy men. When used with GHRP-2 and GHRP-6, sermorelin acetate appears to have a synergistic effect; however, there have been few human studies to examine these effects. There is also a GH secretagogue, macimorelin, that is approved in the US for the diagnosis of adult GHD and is being studied for use in children.

Zero people responded to the survey.

## REFERENCES


1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.
6. Sigalos JT, Pastuszak AW, Allison A, et al. Growth hormone secretagogue treatment in hypogonadal men raises serum insulin-like growth factor-1 levels. *American Journal of Mens Health.* 2017;11(6):1752-1757.
7. Walker RF. Sermorelin: a better approach to management of adult-onset growth hormone insufficiency? *Clinical Interventions In Aging.* 2006;1(4):307-308.
8. Ghigo E, Aimaretti G, Gianotti L, Bellone J, Arvat E, Camanni F. New approach to the diagnosis of growth hormone deficiency in adults. *Eur J Endocrinol.* 1996;134(3):352-356.
9. Valetto MR, Bellone J, Baffoni C, et al. Reproducibility of the growth hormone response to stimulation with growth hormone-releasing hormone plus arginine during lifespan. *Eur J Endocrinol.* 1996;135(5):568-572.
10. Yuen KC, Biller BM, Molitch ME, Cook DM. Clinical review: Is lack of recombinant growth hormone (GH)-releasing hormone in the United States a setback or time to consider glucagon testing for adult GH deficiency? *Journal of Clinical Endocrinology & Metabolism.* 2009;94(8):2702-2707.

## 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 January 31, 2020
- Date last searched: February 3, 2020
- Limits: Humans (search hedge); English language
- Number of results: 268

| | | |
|---|---|---|
| 1 | sermorelin/ | 287 |
| 2 | sermorelin$.tw. | 9 |
| 3 | (growth hormone releasing factor adj2 "29").tw. | 40 |
| 4 | (growth hormone releasing hormone adj2 "29").tw. | 18 |
| 5 | (ghrf adj2 "29").tw. | 4 |
| 6 | (ghrh adj2 "29").tw. | 185 |
| 7 | (somatotropin releasing hormone adj2 "29").tw. | 0 |
| 8 | geref.tw. | 11 |
| 9 | gerel.tw. | 0 |
| 10 | groliberin.tw. | 0 |
| 11 | groliverin.tw. | 0 |
| 12 | or/1-11 | 450 |
| 13 | drug administration routes/ | 5621 |
| 14 | exp administration, intravenous/ | 141779 |
| 15 | infusions, parenteral/ | 26215 |
| 16 | infusions, subcutaneous/ | 1042 |
| 17 | injections/ | 42113 |
| 18 | injections, intra-arterial/ | 9162 |
| 19 | injections, intramuscular/ | 30745 |
| 20 | injections, intravenous/ | 81469 |

| | | |
|---|---|---|
| 21 | injections, subcutaneous/ | 32387 |
| 22 | administration & dosage.fs. | 1389991 |
| 23 | inject$.tw. | 725572 |
| 24 | infusion$.tw. | 241529 |
| 25 | bolus$.tw. | 54093 |
| 26 | (parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw. | 11982 |
| 27 | subcutaneous$.tw. | 162131 |
| 28 | intravenous$.tw. | 334128 |
| 29 | intra venous$.tw. | 566 |
| 30 | intravascular$.tw. | 46761 |
| 31 | intra vascular$.tw. | 298 |
| 32 | intramuscular$.tw. | 51352 |
| 33 | intra muscular$.tw. | 702 |
| 34 | drug therapy/ | 30326 |
| 35 | hormone replacement therapy/ | 9855 |
| 36 | drug effects.fs. | 2943787 |
| 37 | drug therapy.fs. | 2177706 |
| 38 | tu.fs. | 2186863 |
| 39 | therap$.tw. | 2685233 |
| 40 | treat$.tw. | 5321625 |
| 41 | exp diagnosis/ | 8392929 |
| 42 | diagnosis.fs. | 2518838 |
| 43 | diagnos$.tw. | 2381303 |
| 44 | or/13-43 | 16071525 |
| 45 | and/12,44 | 412 |
| 46 | exp animals/ not humans/ | 4669549 |

| | | |
|---|---|---|
| 47 | 45 not 46 | 274 |
| 48 | limit 47 to english language | 268 |

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 3, 2020
- Limits: Humans (search hedge); English language
- Number of results: 351

| | | |
|---|---|---|
| 1 | sermorelin'/de | 315 |
| 2 | sermorelin*':ti,ab,tn | 21 |
| 3 | ('growth hormone releasing factor' NEAR/2 '29'):ti,ab,tn | 38 |
| 4 | ('growth hormone releasing hormone' NEAR/2 '29'):ti,ab,tn | 18 |
| 5 | ('ghrf' NEAR/2 '29'):ti,ab,tn | 5 |
| 6 | ('ghrh' NEAR/2 '29'):ti,ab,tn | 190 |
| 7 | ('somatotropin releasing hormone' NEAR/2 '29'):ti,ab,tn | 0 |
| 8 | geref':ti,ab,tn | 173 |
| 9 | gerel':ti,ab,tn | 0 |
| 10 | groliberin':ti,ab,tn | 20 |
| 11 | groliverin':ti,ab,tn | 1 |
| 12 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 | 499 |
| 13 | drug administration route'/de | 7770 |
| 14 | parenteral drug administration'/de | 2086 |
| 15 | intramuscular drug administration'/de | 71525 |
| 16 | intravascular drug administration'/de | 312 |
| 17 | intravenous drug administration'/de | 391590 |
| 18 | subcutaneous drug administration'/de | 100770 |
| 19 | injection'/de | 215330 |
| 20 | bolus injection'/de | 10855 |
| 21 | drug administration':lnk | 1710786 |
| 22 | inject*':ti,ab | 1077678 |

| | | |
|---|---|---|
| 23 | infusion*':ti,ab | 351148 |
| 24 | bolus*':ti,ab | 77460 |
| 25 | (parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab | 18045 |
| 26 | subcutaneous*':ti,ab | 243619 |
| 27 | intravenous*':ti,ab | 479613 |
| 28 | intra venous*':ti,ab | 1428 |
| 29 | intravascular*':ti,ab | 66669 |
| 30 | intra vascular*':ti,ab | 673 |
| 31 | intramuscular*':ti,ab | 73170 |
| 32 | intra muscular*':ti,ab | 1264 |
| 33 | drug therapy'/de | 705696 |
| 34 | add on therapy'/de | 18424 |
| 35 | hormonal therapy'/de | 44404 |
| 36 | hormone substitution'/de | 36538 |
| 37 | drug response'/exp | 1113962 |
| 38 | drug dose':lnk | 621011 |
| 39 | drug therapy':lnk | 3825733 |
| 40 | therap*':ti,ab | 4048017 |
| 41 | treat*':ti,ab | 7722656 |
| 42 | diagnostic procedure'/exp | 18106899 |
| 43 | diagnosis':lnk | 3191568 |
| 44 | diagnos*':ti,ab | 3637999 |
| 45 | #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 | 24859435 |
| 46 | #12 AND #45 | 462 |
| 47 | [animals]/lim NOT [humans]/lim | 5988861 |
| 48 | #46 NOT #47 | 368 |

| | | |
|---|---|---|
| 49 | #46 NOT #47 AND [english]/lim | 351 |

*Appendix 2.1. Survey instrument for use of sermorelin acetate alone*

Welcome. We want to understand your clinical use of compounded sermorelin acetate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

| | Very familiar | Somewhat familiar | Not familiar |
|---|---|---|---|
| Compounded drugs (medications prepared to meet a patient-specific need) | o | o | o |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | o | o | o |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | o | o | o |

2. Do you prescribe or administer sermorelin acetate to your patients?

   - o Yes
   - o No

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

   - o Growth hormone deficiency
   - o Other (please explain) _____

4. I use sermorelin acetate with my patients as the following: (check all that apply)

   - o FDA-approved drug product
   - o Compounded drug product
   - o Over-the-counter drug product
   - o Dietary supplement (e.g. vitamin or herbal supplement sold in retail)
   - o Other (please describe)_____

5. I use compounded sermorelin acetate because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain)_____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing sermorelin acetate.
    - o Other (please explain) _____

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

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

7. I obtain compounded sermorelin acetate from the following: (check all that apply)

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

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 use of sermorelin acetate in combination*

Welcome. We want to understand your clinical use of compounded growth hormone releasing peptide-2 (GHRP2/Pralmorelin) in combination with GHRP6 and sermorelin acetate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

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OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

| | Very familiar | Somewhat familiar | Not familiar |
|---|---|---|---|
| Compounded drugs (medications prepared to meet a patient-specific need) | o | o | o |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | o | o | o |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | o | o | o |

2. Do you prescribe or administer GHRP2 / GHRP6 / sermorelin acetate to your patients?

   - o Yes
   - o No

3. I prescribe or administer GHRP2 / GHRP6 / sermorelin acetate 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 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.
   - o Other (please explain) _____

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

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

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

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

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

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

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

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

*Appendix 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.