

## Sermorelin in the Management of Age-Related Growth Hormone Insufficiency

### Introduction and Background

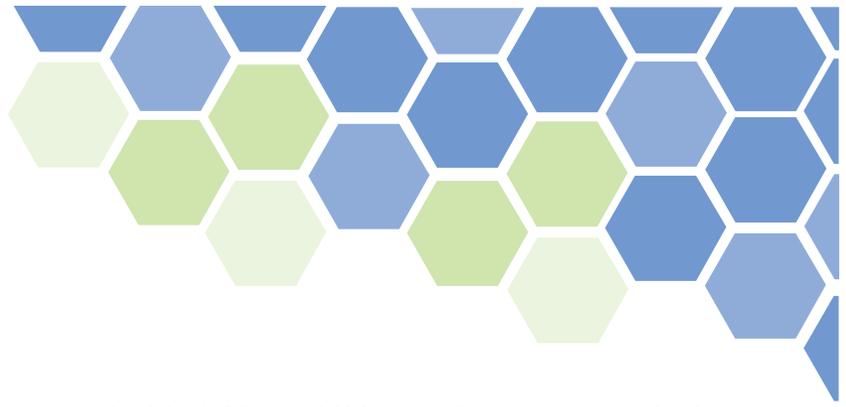
**Growth Hormone Replacement:** Growth hormone replacement therapy (GHRT) is a regimen for treating physical and functional problems in people whose bodies, for one or more reasons fail to produce adequate somatotropin (somatotropin, human growth hormone, hGH). During aging there occurs a progressive decline of hGH production which fails to maintain essential aspects of bodily form and function that are needed for a healthy life of normal duration.



The medical condition resulting from inadequate production and/or utilization of hGH is called growth hormone deficiency (GHD)<sup>1</sup>. GHD was initially observed in children where it sometimes occurs because of problems in the brain and pituitary gland<sup>2,3</sup>. These significantly affect growth and development and also cause medical problems and reduced quality of life. Thus, childhood-onset GHD has been treated with GHRT for more than 30 years. In the past, hGH therapy in children affected by GHD was stopped when bone growth ceased upon their reaching final height. This focus on height originally reflected a measure of successful GHRT after which treatment was ended. This was done, in part because hGH was originally extracted from human cadavers making its supply limited. However, with advances in genetics

it became possible to clone the gene capable of producing hGH in cell culture. Thereafter, the recombinant form of human growth hormone (rhGH) became available in unlimited quantities. Because of its availability for clinical application, rhGH became the drug of choice, not only because of its efficacy, but also because it avoids the risk of transmitting a fatal virus that was sometimes associated with the cadaver-derived hormone<sup>4</sup>.

Although originally indicated for use in childhood GHD, rhGH became a licensed indication for GH-deficient adults in the United States, a number of European countries, and New Zealand in 1996.



This action was taken because people who had been treated with rhGH as children and then were routinely discontinued from treatment upon reaching final height, experienced higher than expected rates of medical problems as adults, beginning in their 30s and 40s. These included reduced physical, mental, and social energy, excess adipose tissue, diminished muscle mass, diminished libido, poor bone density, higher than normal cholesterol levels, and elevated rates of cardiovascular disease.

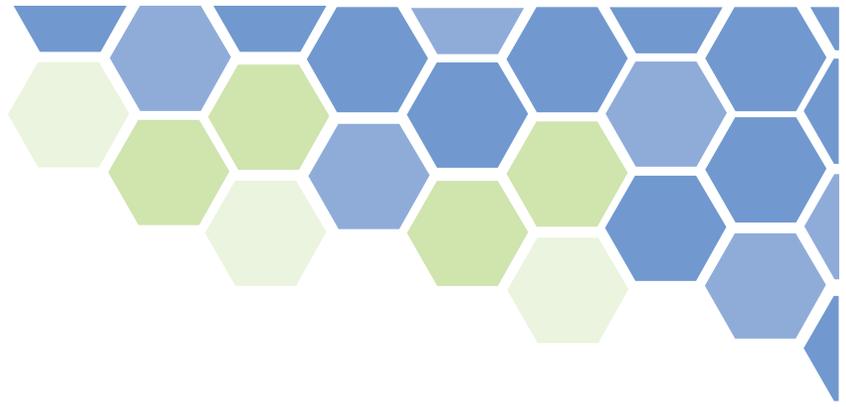
Research trials soon confirmed that a few months of GH replacement therapy could improve nearly all of these parameters in GHD patients. Coincidentally, it was noticed that the same changes in body composition and the increased risk for metabolic diseases also occur spontaneously as men and women grow older<sup>5</sup>! The progressive age-associated decline in hGH production and its associated medical problems is collectively known as the somatopause. The term represents cessation of optimal secretion of hGH which is similar to the decline of reproductive hormones that occur during the menopause in women and the andropause in men.

However, there are causal differences between childhood-onset and adult-onset GHD (AGHD) when compared with progressive, age-related GHD. Initial investigations into the causes of adult onset GHD showed them to result from damage to the pituitary gland resulting from tumors, surgery or radiotherapy that disrupted function of the tissues that produce and secrete hGH<sup>6,7</sup>. Since age-related GHD is not associated with these causes, nor is aging generally considered a “disease”, there has been reticence to diagnose and treat GHD in the obese and in the elderly as it has been treated in children and those suffering from AGHD<sup>8-10</sup>.

Thus at first, little attention was paid to treating the progressive decline in hGH production that results in clinical symptoms similar to those associated with classical GHD as the body ages. To differentiate the causes of low hGH in adults, the age-related decline in hGH production is often called GH insufficiency (GHI) to distinguish it from originally described GHD.

For these reasons, administration of rhGH which is the accepted treatment for AGHD, has not been permitted for use in aging by the FDA. This is true even though insulin-like growth factor-1 (IGF-1), a hormone in the blood that is an indirect marker for hGH production and secretion is indistinguishable in normal aging people after age 40 years from those with AGHD. Nonetheless, the FDA restricts in part, diagnosis of GHD and treatment with rhGH to those under 40, and thereby requires different treatments for medical issues related to age-associated GHI.

Thus, because of the effects of aging that occur during middle and later stages of life resulting in GHI, endocrine therapies for treating it have been sought over the past two decades<sup>11</sup>. In fact, many years of off-label use of sermorelin, a GH secretagogue, has improved the life and health of many suffering from progressive and degenerative conditions of aging.



**Somatopause:** Many of the body's systems that function to maintain optimal health and well-being decline with advancing age. Aerobic capacity, muscle mass, and strength all progressively decline with age. Loss of muscle mass, or sarcopenia, and the accompanying reduction in strength increases the risk of falls and their complications, and for many individuals the associated loss of physical, functional capacity leads to increasing difficulty in living independently. Complaints of poor sleep are common in older populations. Insomnia reduces quality of life and is often a factor in decisions to seek health care. Sleep complaints often lead to overmedication and sedation of the elderly that is often associated with increased morbidity and mortality.

Finally, brain function declines with advancing age, particularly in those cognitive functions that involve novel problem solving and psychomotor processing speed. These deficits in turn also impact on the older individual's ability to live independently<sup>12</sup>.

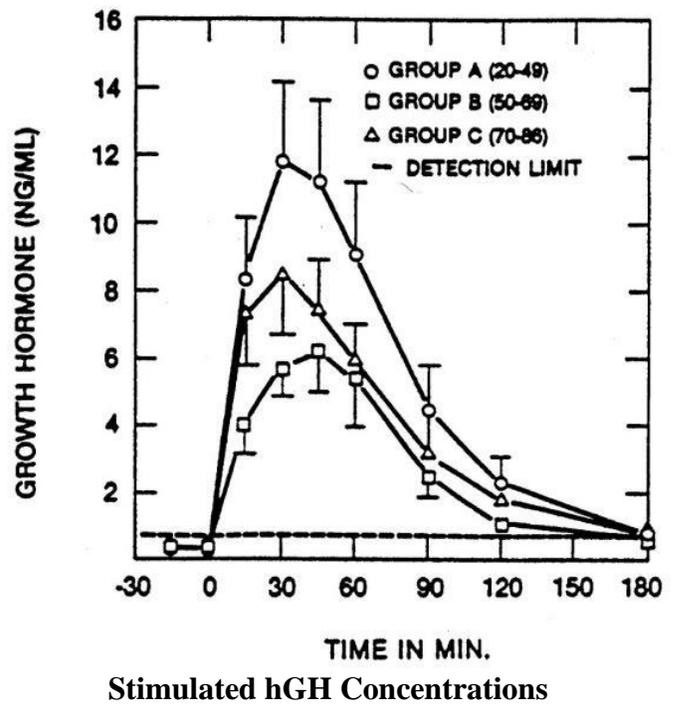
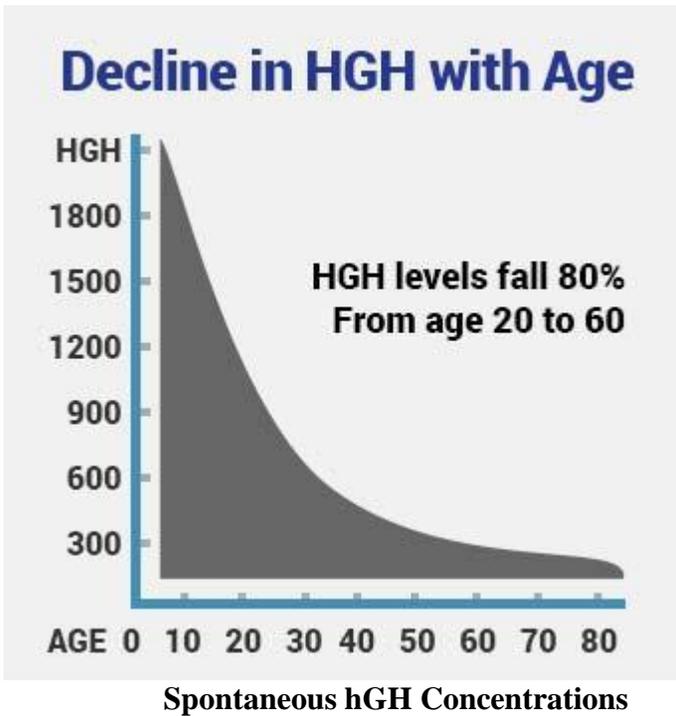
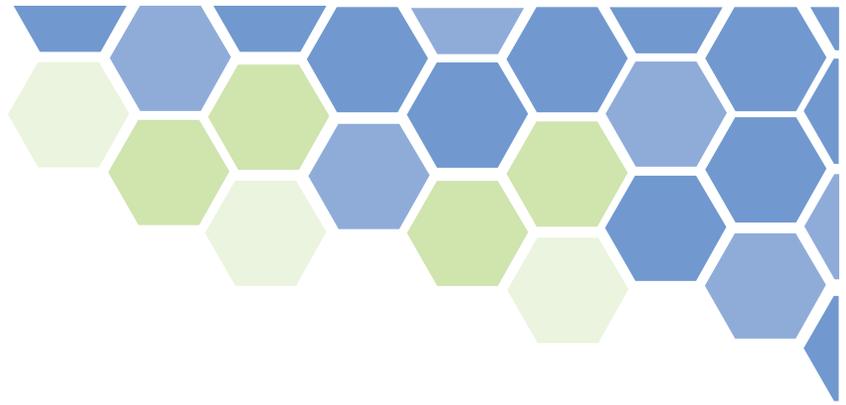
**Progressive loss of muscle mass, strength and function is a hallmark of the aging.**



*During development until young adulthood, muscles grow larger and stronger.  
But after 30 years of age muscle mass and function slowly decline.*

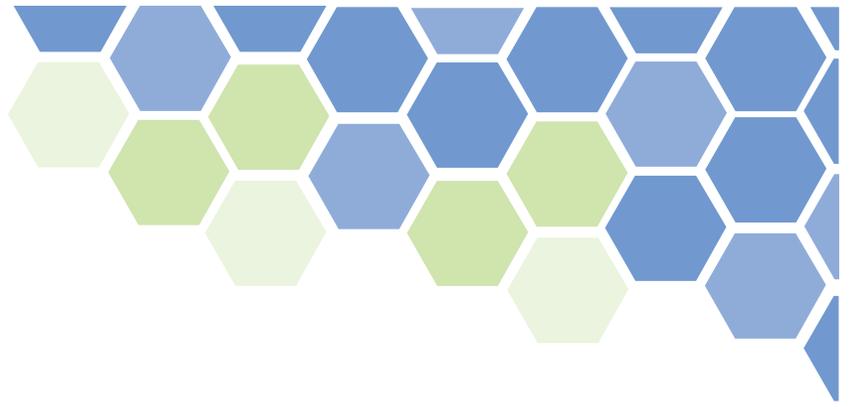
Aging in both sexes is accompanied by profound decreases in serum hGH and IGF-I concentrations. These effects are directly attributed to reduced activity of an area in the brain that produces GH-releasing hormone (GHRH), the hormone that stimulates hGH production. At the same time, secretion of somatostatin (SRIF), a brain hormone that inhibits hGH increases<sup>13-15</sup>.

As a result, hGH secretion declines from a peak during puberty to about one-tenth of that value by age 55. Circulating hGH levels are lower and stimulated hGH is blunted during aging<sup>16,17</sup>.

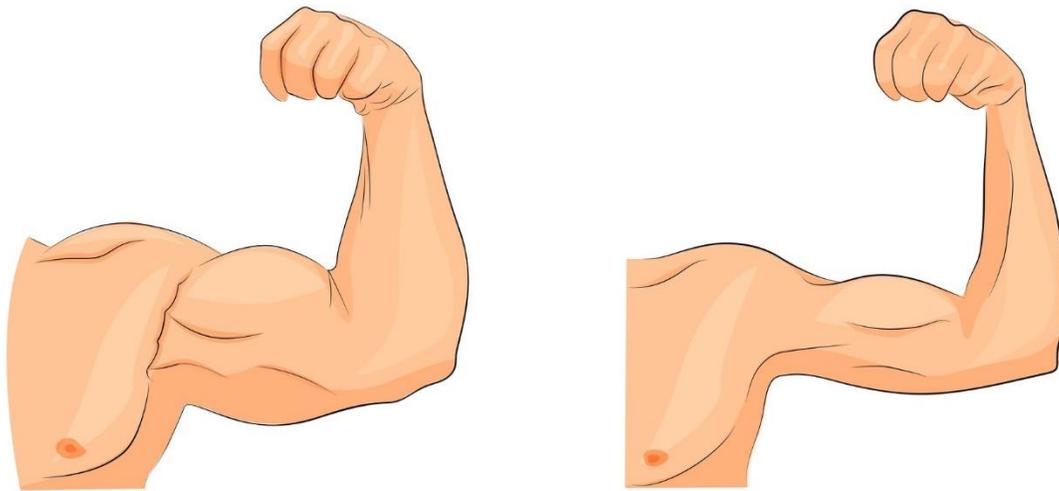


During this process there is a reduction in the pattern of hGH sleep-related GH secretion resulting in loss of a clear night-day hGH rhythm<sup>18-19</sup>. The decline in GH production parallels the age-related decline in body mass index and is associated with alterations in body composition, hormonal status, and functional capacity that mimic the changes seen in GHD<sup>20</sup>.

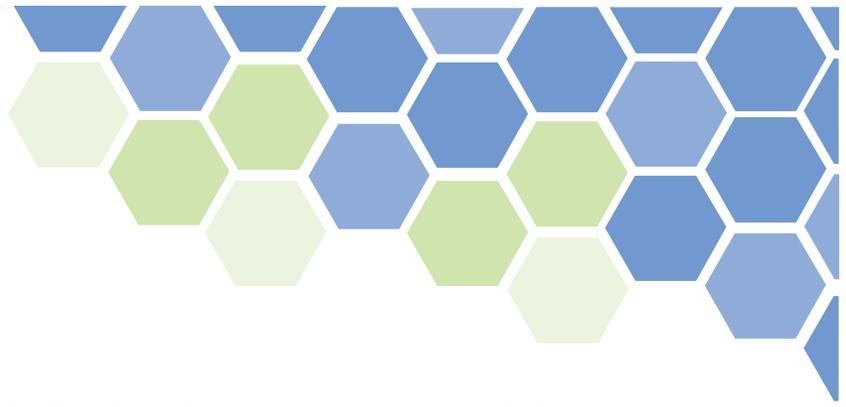
In addition to deteriorating memory and cognitive function, the changes in body composition that are most pronounced in normal aging include a reduction in bone density and in muscle mass and strength, an increase in body fat, and adverse changes in lipoprotein profiles<sup>21,22</sup>. The decline in hGH production is not evident initially, but over time contributes to sarcopenia (severe loss of muscle) and frailty.



**People who are physically inactive can lose as much as 3% to 5% of their muscle mass per decade after age 30. But, even those who are active still experience some muscle loss.**



*Loss of muscle mass accelerates significantly in middle age and beyond regardless of physical activity, albeit more rapidly with inactivity.*



Since GH secretion declines progressively and markedly with aging, and many age-related changes resemble those of adult-onset GHD, stimulating production and secretion of the body's own hGH with GH-releasing hormone (GHRH) or its analog Sermorelin could confer benefits in normal aging similar to those observed by treatment with rhGH. In particular, such treatment could reduce the loss of muscle mass, strength, and exercise capacity that leads to frailty; thereby prolonging the ability to live independently.

**Pharmaceutical Secretagogue Products:** Growth hormone secretagogues (GHSs) are a class of molecules that stimulate the secretion of hGH from the pituitary gland<sup>23</sup>. They include stimulators of brain and pituitary receptors for GHRH such as Sermorelin.

## About Sermorelin

**Sermorelin** is a synthetic (man-made) version of naturally occurring GHRH that can be used clinically to stimulate release of growth hormone (GH) from the pituitary gland<sup>23</sup>. Growth hormone is necessary for growth in children and is important in adults to maintain metabolic and physiologic functions that are necessary for good health and quality of life. Thus, Sermorelin can be effective in cases of GHI and thereby sustain essential bodily functions throughout life

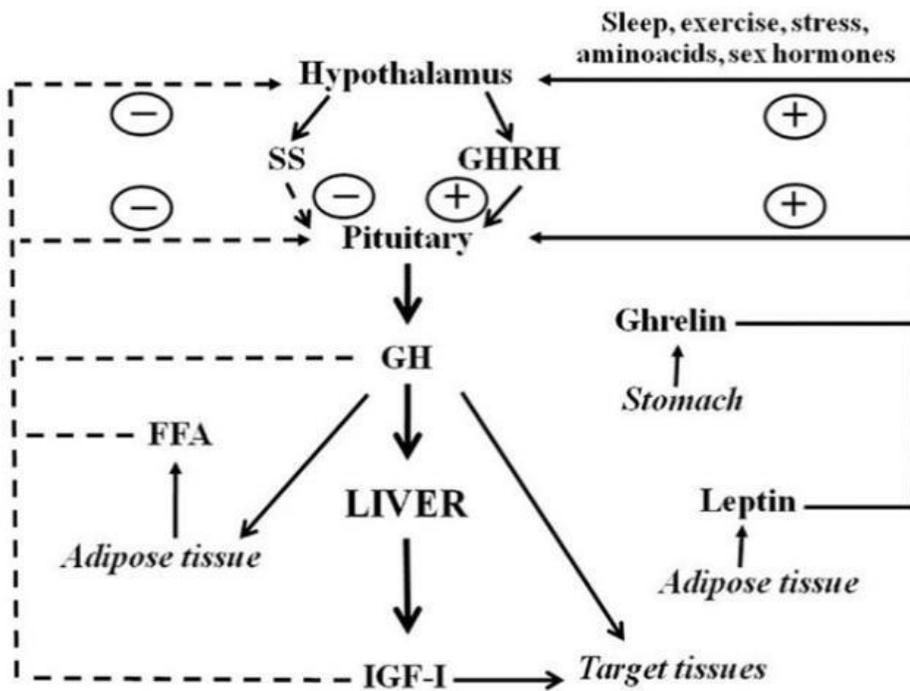
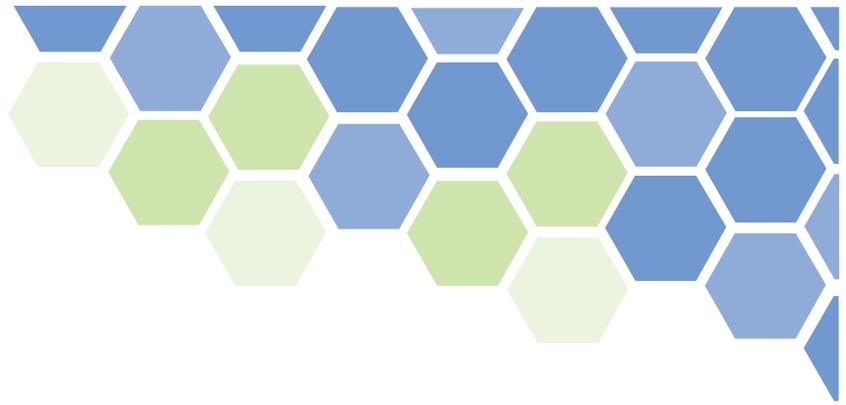
**Pharmacologic Class:** Sermorelin is a shortened form of GHRH. It consists of the first 29 amino acids of the naturally occurring neurohormone that is produced in an area of the brain called the hypothalamus<sup>23</sup>.

**Therapeutic class:** Endocrine-Metabolic Agent (Growth hormone (GH) releasing hormone)

**Nomenclature:** Sermorelin acetate, Geref, GRF<sup>1-29</sup>, GRH-NH<sup>2</sup> or GRF-NH<sup>2</sup>

**Clinical Applications:** Some uses for Sermorelin include: Diagnosis of growth hormone deficiency/insufficiency (GHD/GHI)<sup>24</sup>, treatment of children with some forms of growth hormone deficiency<sup>25</sup>, management of adult-onset GHD/GHI and other conditions requiring GH replacement therapy (GHRT)<sup>25,26</sup>, regeneration of pituitary function and delay its functional decline during aging<sup>27,28</sup>.

**General Information:** Sermorelin is the most widely used member of the GHRH secretagogue family of molecules. It can significantly promote the synthesis and hGH from cells in the pituitary gland, increasing serum concentrations of hGH and subsequently IGF-1<sup>29,30</sup>. It is able to influence the complex of hormonal signals that affect hGH secretion including GHRH, somatostatin, insulin like growth factors and others.



Since the positive and negative opposing influences of GHRH and somatostatin on hGH creates a rhythmic pattern of its secretion, improvement in GH secretion profiles results from Sermorelin administration.

After sermorelin stimulates the release of hGH from the pituitary gland, synthesis of IGF-1 is increased in the liver and peripheral tissues<sup>31</sup>.

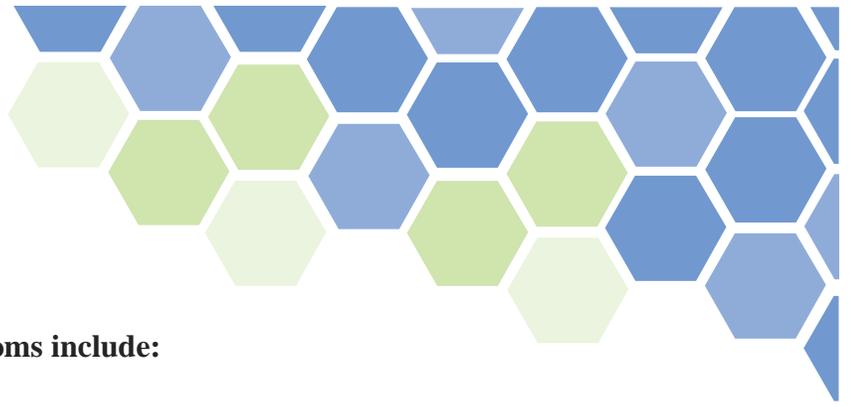
Sermorelin is degraded in approximately 10 to 20 minutes after reaching the bloodstream. A single daily dosing is sufficient to treat most cases of age-related GHI.

In addition to increasing production and secretion GHRH also affects sleep patterns by increasing the amount of slow wave sleep (SWS) while augmenting sleep-related GH secretion and reducing cortisol secretion.

specific receptor on pituitary cells called somatotrophs, that produce hGH<sup>32</sup>. Thereafter, it turns on the gene that synthesizes hGH and also increases cellular activity to facilitate secretion of hGH<sup>33</sup>. Sermorelin also increases proliferation of somatotroph cells in the pituitary gland during development<sup>34,35</sup>.

Symptoms of Adult Growth Hormone Deficiency/Insufficiency: Adults with inadequate concentrations of serum GH can have a variety of signs and symptoms, some of which include abnormal body composition, reduced fluid volume, diminished strength, physical energy and stamina, lack of motivation, lethargy, lability etc.

While symptoms of growth hormone deficiency/insufficiency in adults can vary, many experience a combination of the symptoms below that progress in number and intensity with advancing age<sup>36</sup>.



### **Age-related growth hormone deficiency symptoms include:**

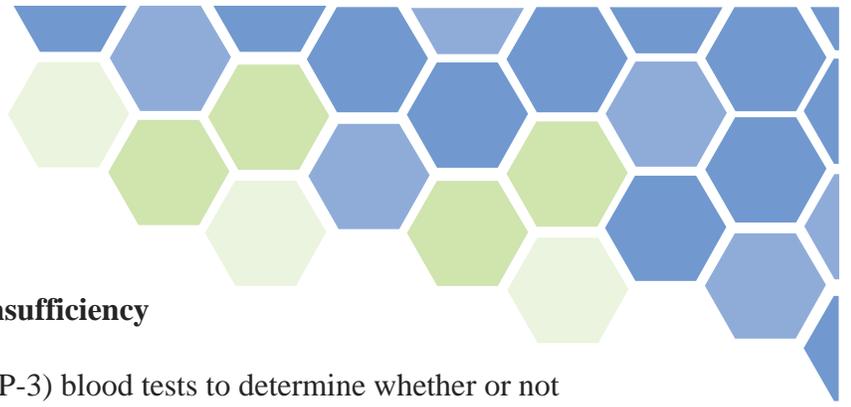
- Baldness (in men)
- Anxiety and/or depression
- Decrease in sexual function and interest
- Decreased muscle mass and strength
- Difficult to concentration and lack of memory
- Dry, thin skin
- Elevated triglyceride levels
- Fatigue and/or tiredness
- Heart problems
- High levels of LDL (the “bad”) cholesterol
- Insulin resistance
- Lower tolerance to exercise
- Reduced bone density, making you more susceptible to developing osteoporosis
- Sensitivity to heat and cold
- Very low energy levels
- Weight gain, especially around the waist

### **Diagnosis of Adult Growth Hormone Deficiency**

Not everyone with GHD/GHI will have the same symptoms. Some people will only have one or two while others can have multiple symptoms. Fortunately, certain tests and exams can help physicians to make an appropriate diagnosis. Exams and tests used to diagnose growth hormone deficiency are the same no matter the patient’s age.

Diagnosing GHD/GHI typically starts with a physical exam. The physician checks weight, height, and body proportions. Other than a physical exam, there are many other tests and exams used to make a growth hormone deficiency diagnosis.

Some or all of the following tests can be used to diagnose age related GHI since everyone will be so affected over the course of their lives. Such diagnostic testing may be used to determine the degree to which replacement therapy is indicated, i.e., for dosing determinations.



## Blood Tests for Growth Hormone Deficiency/Insufficiency

- Binding protein level (IGF-I and IGFBP-3) blood tests to determine whether or not the problem is caused by the pituitary gland
- Blood tests to measure the amount of growth hormone levels in the blood
- Blood tests to measure other levels of hormones the pituitary gland produces
- GHRH (Sermorelin)-arginine provocative test
- Other GH provocative stimulation tests
- Insulin tolerance test
- If an individual experiences signs and symptoms of GHD/GHI, he/she should talk to a doctor so as to perform exams and tests that assist in making an accurate endocrine analysis and diagnosis.

## Treatment of GHI

While aging is not a disease, it results in significantly maladaptive changes in body composition and function that affect the individual and the community at large. While aging is associated with a milder form of adult GHD, GH replacement with secretagogues such as Sermorelin has met with success. Once daily injections can stimulate increases in GH and IGF-I at least to the lower part of the young adult normal range<sup>37,38</sup>. Because peptides like Sermorelin are readily destroyed by enzymes in the digestive tract, subcutaneous (SC) or intravenous (IV) injections are the only way to administer the molecule.

Since IV injections are impractical for most people, the SC route is commonly used to administer doses of Sermorelin ranging between 0.2 – 1.0 mg per day. The most commonly used dosage is 0.5 mg daily. In a University of Washington study consisting of 6 months treatment with daily bedtime subcutaneous injections of Sermorelin, alone or in combination with supervised exercise conditioning, IGF-I levels rose approximately 35%. Subjects showed an increase in lean body mass and a decrease in body fat (particularly abdominal visceral fat)<sup>39,40</sup>.

Such changes indicate that regular GHRT with Sermorelin can resist changes in body composition underlying sarcopenia and frailty that lead to loss of independence. Thus, since the aging pituitary remains responsive to GH and GHSs, it is reasonable that stimulation with Sermorelin is indicated in aging<sup>38</sup>.

While elders are more sensitive to GH, and thus more susceptible to the side effects of replacement with rhGH, the use of Sermorelin to stimulate production and secretion of endogenous GH offers the advantage of a more physiological approach to increasing rhythmic hGH secretion while reducing risk for side effects.



**Key warnings before taking this medicine:** Tell your doctor your medical history, especially of thyroid problems, brain disorders (e.g., lesions) and any allergies. Discuss the risks and benefits with your doctor regarding use in pregnant women. It is not known whether this drug passes into breast milk. Because of the potential risk to the infant, breast-feeding while using this drug is not recommended. Consult your doctor before breast-feeding.

**How is it best taken?**

Inject this medication subcutaneously before bedtime, or as directed by your healthcare provider.

**What do I do if I miss a dose?**

If you miss a dose, use it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

**What are the precautions for taking this medicine?** Tell your doctor of all prescription and nonprescription medications you may be using, especially corticosteroids and thyroid medications. This drug may affect the results of certain lab tests e.g., inorganic phosphorus, alkaline phosphatase. Make sure laboratory personnel and your doctors know you use this drug. Do not start or stop any medicine without approval from your healthcare provider.

Untreated hypothyroidism can jeopardize the response to Sermorelin. Thyroid hormone determinations should be performed before initiating and while receiving therapy. Thyroid hormone replacement therapy should be initiated only when indicated.

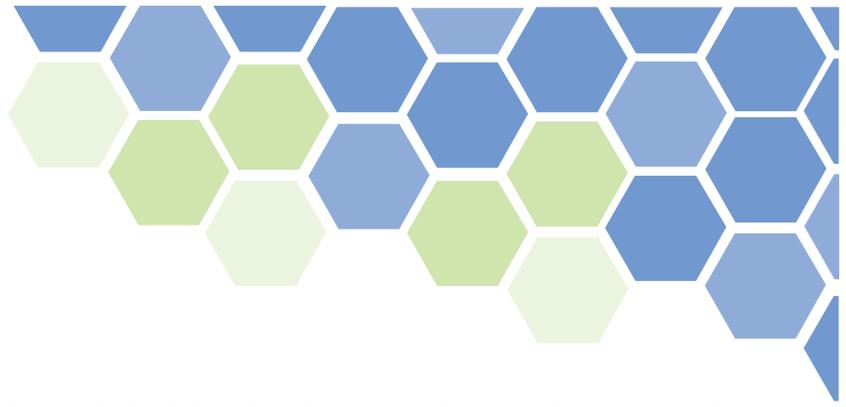
Patients with GHD secondary to an intracranial lesion were not studied in clinical trials. Thus, Sermorelin treatment is not recommended in such patients.

Subnormal GH responses have been seen in obesity and hyperglycemia, and in patients with elevated plasma fatty acids.

The FDA pregnancy risk category C. Exercise caution during lactation; it is not known if this drug is excreted in breast milk.

**Laboratory Tests:** Serum levels of inorganic phosphorus, alkaline phosphatase, GH and IGF-I may increase with therapeutic use.

**Corticosteroids:** Glucocorticoids may inhibit the response to Sermorelin. Controlled studies did not indicate an interaction of Sermorelin with drugs commonly used in the treatment of routine medical problems/illnesses. However, formal drug interaction studies have not been conducted.



**General Warnings:** hGH is traditionally contraindicated in individuals with benign intracranial hypertension (BIH), critically ill persons (e.g., after complications following open heart or abdominal surgery, multiple trauma, acute respiratory failure or similar conditions), diabetic retinopathy, and persons with evidence of tumor activity. In persons with tumors, anti-tumor therapy must be completed before initiating hGH therapy. Persons with known hypersensitivity to hGH or to any of its excipients, women who are pregnant, planning to become pregnant, or lactating should not use this product.

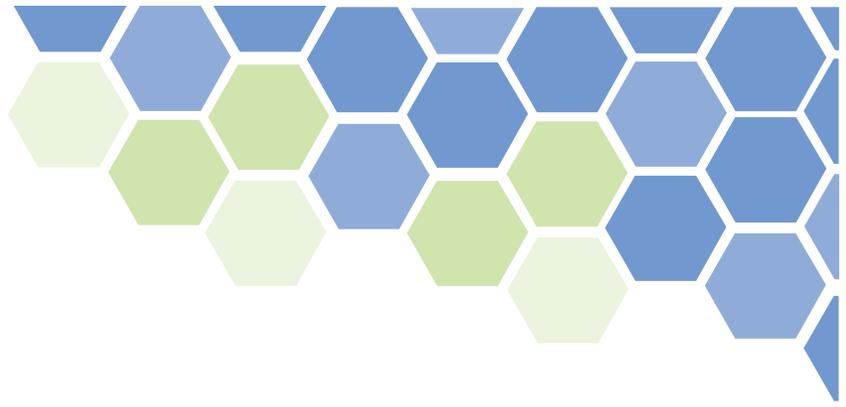
**Possible Side Effects:** Call your doctor for medical advice if pain/swelling/redness occurs at the injection site (occurring in approximately 16% of patients). Other possible, but less common side effects of rhGH (not reported for Sermorelin) are upper respiratory conditions, nerve sensitivity, insomnia, depression, nausea, hypothyroidism chest pain, gynecomastia, headache, flushing, dysphagia, dizziness, hyperactivity, somnolence, urticaria and sore bones. Call your health care provider immediately if you are experiencing trouble swallowing, vomiting, and tightness in the chest.

Antibody formation to Sermorelin has been reported after chronic subcutaneous administration of large doses but their clinical significance is unknown. Antibodies do not appear to affect growth hormone release nor appear to be related to a specific adverse drug reaction profile.

No generalized allergic reactions have been reported. A temporary allergic reaction described by severe redness, swelling and urticaria at the injection sites has been reported in one patient who developed antibodies. Additionally, its use may reduce insulin sensitivity, thereby raising blood sugar to levels which could be harmful to diabetes sufferers.

It may also decrease triiodothyronine (T3) levels due to its tendency to reduce the bodily levels of sodium, potassium, and phosphorous. How should I store this medicine? Keep this medicine in a refrigerator below 41°F (5°C). If precipitates form within the solution, warm a cup of water to 90°C and place the vial into the warm water until the precipitates dissolve. Keep all medicine out of the reach of children. Throw away any unused medicine after the expiration date. Do not flush unused medications nor pour them down a sink or drain.

**General statements:** Do not share or take anyone else's medicine. Talk with your healthcare provider before starting any new medicine, including over-the-counter, natural products, or vitamins. This medication was compounded specifically for you. This patient information summarizes the most important information about your medication; if you would like more information, speak with your doctor.



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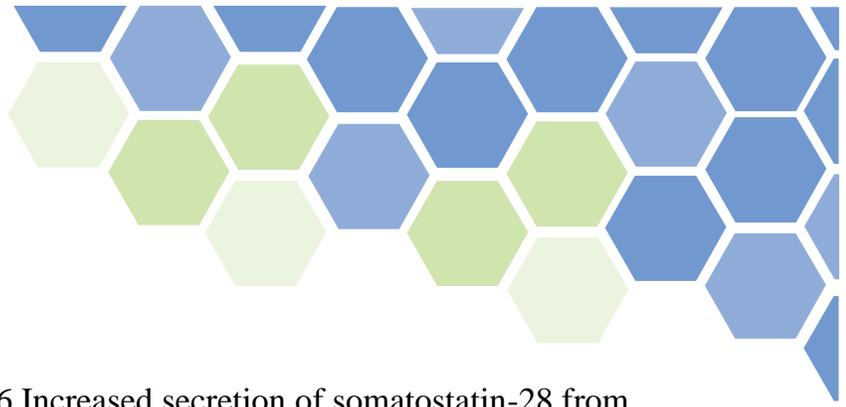
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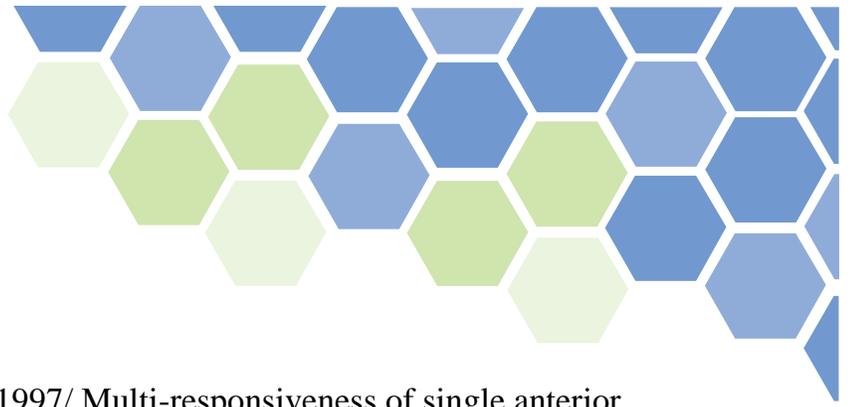
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