# Ipamorelin Acetate
# for Growth Hormone Replacement Therapy

## Introduction and Background

Several decades ago, clinical research trials confirmed that administration of human growth hormone (hGH) for a few months improved nearly all maladaptive symptoms of growth hormone deficiency (GHD) resulting from frank damage to the brain and pituitary as well as those associated with somatopause insuffiency. Somatopause is commonly used to describe cessation of optimal secretion of human growth hormone (hGH) during aging, which can be likened to the decline of reproductive hormones that occur during the menopause in women and the andropause in men.

The decline in GH production by the body 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[1]. 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[2,3]. The decline in hGH production is not evident initially, but over time contributes to sarcopenia (severe loss of muscle) and frailty.

Unlike pathologic, adult-onset GHD (AGHD), which progresses from childhood to maturity, age-related GHD is not associated with overt damage to the brain or pituitary gland, nor is it aging generally considered a “disease”. Nonetheless, age-related GHD has the same negative impact on the body as does AGHD and would respond positively to treatment with recombinant hGH if there were no restrictions on its use.

However, there are certain risks associated with regular use of recombinant hGH in treating symptoms of the somatopause. These include increased risk for cancer, cardiovascular disease, and behavior changes. The non-physiological, unregulated effect of hGH can stimulate overproduction of insulin like growth factor (IGF-1) that can lead to carpal tunnel syndrome and arthritis-like symptoms, diabetes, abnormal growth of the bones and internal organs, high blood pressure and hardening of the arteries.

Thus, the American Association of Clinical Endocrinologists warns against its use to diagnose and treat symptoms of the somatopause and administration of rhGH has been prohibited from use in aging by the FDA.

While potentially beneficial, the dangers of regularly administered rhGH result from the body's inability to control its effects through feedback mechanisms, a series of hormonal checks and balances that normally maintain optimal hGH levels in the body. Fortunately, over the past several decades, secretagogues that can safely improve your body's ability to produce its own hGH without the side effects of hGH injections have been developed[4].

## Growth Hormone Secretagogues

At approximately the same period of time, i.e., the late 1970's and early 1980, two families of GH secretagogues (GHSs) were developed and became available for clinical application. These molecules are peptides analogs of two different endogenous molecules that normally regulate secretion of hGH through different actions in the brain and pituitary[5,6].One family is represented by a structurally altered form of growth hormone releasing hormone (GHRH) while the other family contains small peptides that mimic the action of ghrelin but bear no structural similarity to the native hormone.

GHRH was originally extracted from human tissue and then its structure was truncated to contain only the first 29 amino acids. This fragments was called Sermorelin and it is the active part of naturally occurring, whole molecule. In contrast, the first growth hormone-releasing peptides (GHRP) were invented rather than isolated from biological material. Met-enkephalin which is sometimes referred to as opioid growth factor (OGF), a pentapeptide with the amino acid sequence tyr-gly-gly-phe-met, was used as a template from which GHRPs were invented[7]. Modification of met-enkephalin involved substitution of unnatural, dextrorotatory (D-) isomers of certain amino acid for those that were naturally occurring[8,10]. These unique amino acids are not vulnerable to enzymatic degradation and so, offered the potential for oral or nasal administration. The first potent example to be developed was the hexapeptide GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH2) which releases GH in vitro and in vivo[1-16]. Over time the GHRP family grew to include more potent analogs including a heptapeptide, GHRP-1 (Ala-His-Dbeta-NaI-Ala-Trp-D-Phe-Lys-NH2). and two hexapeptides, GHRP-2 (D-Ala-D-beta-Nal-Ala-Trp-D-Phe-Lys-NH2) and Hexarelin (His-D-2-methyl-Trp-Ala-Trp-D-Phe-Lys-NH2).

All of these GH secretagogues released GH with varying degrees of potency. However, addition to GH, they also increased prolactin (PRL) and cortisol secretion, indirectly by stimulating pituitary release of adrenocorticotrophin (ACTH). These hormones counteracted the beneficial effects of hGH on lean body mass. Thus, in an attempt to circumvent this undesirable characteristic of the GHRP's a new series of GHRP receptor-active GH secretagogues was developed at Novo Nordisk by Raun and associates[17].

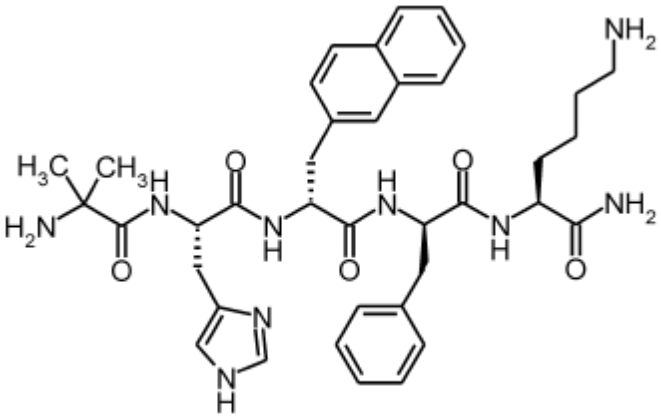
# Ipamorelin: Review of Salient Points

Ipamorelin like Sermorelin is a peptide that functions as a growth hormone releaser in the brain and pituitary gland. Synthetically created in lab settings, these peptides turn on the gene responsible for GH synthesis thereby increasing the amount of growth hormone to be produced and secreted by the pituitary gland. Increased growth hormone has been found to help prevent stunted growth, in test animals that are lacking this hormone, as well as have influence on injury recovery time, tissues functionality, and regulate the metabolism.

**What is Ipamorelin**

Functioning as a secretagogue, Ipamorelin binds to receptors in the brain and pituitary cells to cause the production and release of growth hormone. Not only does it stimulate the pituitary gland to release growth hormone, it also inhibits the release of somatostatin. Ipamorelin creates a steadier slow release of growth hormone and as such mimics the natural release of GH. In laboratory studies it is shown that Ipamorelin has a more stable release of GH than most other GHRPs. In studies previously done on animal test subjects, it was found that Ipamorelin has the ability to strengthen connective tissue and joints, bone strength, and metabolism.

# Ipamorelin Family, Structure and Pharmacokinetics



ipamorelin

A prototype of a new series of ghrelin-type secretagoges, Ipamorelin was developed by NovoNordisk and found to be potent, selective and efficacious in several species[17]. It resulted from significant modification of the typical GHRP peptide structure in that it lacked two central amino acids (Alanine [ALA] and Tryptophan [TRP]) at positions 4 and 5 that were originally thought to be necessary for activity of GHRP peptides[18]. Surprisingly, when these amino acids were removed and the molecule substituted with a non-proteinogenic amino acid called alpha amino butyric acid (Aib) that is rather rare in nature, ipamorelin displayed significant activity *in vitro* and *in vivo*. Aib is a strong helix inducer in peptides which may contribute to the favorable pharmacokinetic profile of ipamorelin. As a result of this substitution and the addition of "unnatural" amino acids to the molecule including , D-2-napthylalanine (D-2-Nal) and D-Phenlyalanine (D-Phe), the resultant structure, *Aib-His-D-2-Nal-D-Phe-Lys-NH2*, offered resistance to enzymatic cleavage and unique efficacy as a growth hormone secretagogue. . The modification of typical GHRP structure in ipamorelin is shown in Figure 1 which identifies the absence of Ala and Trp along with the addition of alpha-amino-alpha butyric acid (Aib)[19].

**Table 1.** Elemental composition of GHRPs and their metabolites.

| | | POSITION AT GENERAL SEQUENCE | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| COMPOUND CODE | TRIVIAL NAME | 1 aa- | 2 aa- | 3 aa- | 4 Ala- | 5 Trp- | 6 (D-Phe)- | 7 Lys- | C-terminal form $NH_2$/OH |
| 1 | GHRP-1 | Ala- | His- | (D-β-Nal)- | Ala- | Trp- | (D-Phe)- | Lys- | $NH_2$ |
| 2 | GHRP-1 (2-7) | - | His- | (D-β-Nal)- | Ala- | Trp- | (D-Phe)- | Lys- | $NH_2$ |
| 3 | GHRP-1 (2-7) FA | - | His- | (D-β-Nal)- | Ala- | Trp- | (D-Phe)- | Lys- | OH |
| 4 | GHRP-1 (3-7) | - | - | (D-β-Nal)- | Ala- | Trp- | (D-Phe)- | Lys- | $NH_2$ |
| 5 | GHRP-1 (3-7) FA | - | - | (D-β-Nal)- | Ala- | Trp- | (D-Phe)- | Lys- | OH |
| 6 | GHRP-1 (3-6) FA | - | - | (D-β-Nal)- | Ala- | Trp- | (D-Phe)- | - | OH |
| 7 | GHRP-2 | - | D-Ala- | (D-β-Nal)- | Ala- | Trp- | (D-Phe)- | Lys- | $NH_2$ |
| 8 | GHRP-4 | - | - | (D-Trp)- | Ala- | Trp- | (D-Phe)- | - | $NH_2$ |
| 9 | GHRP-4 FA | - | - | (D-Trp)- | Ala- | Trp- | (D-Phe)- | - | OH |
| 10 | GHRP-5 | - | Tyr- | (D-Trp)- | Ala- | Trp- | (D-Phe)- | - | $NH_2$ |
| 11 | GHRP-6 | - | His- | (D-Trp)- | Ala- | Trp- | (D-Phe)- | Lys- | $NH_2$ |
| 12 | HEXARELIN | - | His- | (D-Mrp)- | Ala- | Trp- | (D-Phe)- | Lys- | $NH_2$ |
| 13 | HEXARELIN FA | - | His- | (D-Mrp)- | Ala- | Trp- | (D-Phe)- | Lys- | OH |
| 14 | HEXARELIN (2-6) | - | - | (D-Mrp)- | Ala- | Trp- | (D-Phe)- | Lys- | $NH_2$ |
| 15 | ALEXAMORELIN | Ala- | His- | (D-Mrp)- | Ala- | Trp- | (D-Phe)- | Lys- | $NH_2$ |
| 16 | IPAMORELIN | Aib- | His- | (D-2-Nal)- | | | (D-Phe)- | Lys- | $NH_2$ |
| 17 | IPAMORELIN FA | Aib- | His- | (D-2-Nal)- | | | (D-Phe)- | Lys- | OH |
| 18 | IPAMORELIN (1-4) FA | Aib- | His- | (D-2-Nal)- | | | (D-Phe)- | - | OH |

To determine whether ipamorelin truly represented a novel form of ghrelin analogs, the binding specificity of the peptide was investigated using antagonists to the GHRP receptor (D-Lys3)-GHRP-6, L-692,400 and (D-Arg1,D-Phe5,DTrp7,9, Leu11)-Substance P, and also of the GHRH receptor N-Acetyl-Tyr1,D-Arg2)-hGHRH(1–29)NH2, respectively, to determine whether either of the antagonists affected stimulation by ipamorelin. The GHRP antagonists had no effect on GHRH-induced GH release whereas the GH releasing effects of both GHRP-6 and ipamorelin were inhibited with similar potencies. In contrast, the GHRH antagonist (N-Acetyl-Tyr1,D-Arg2)-hGHRH(1–29)NH2 potently inhibited GHRH-induced GH release, but had no effect on GH release induced by either GHRP-6 or ipamorelin.

This clearly suggests a GHRP receptor agonist profile of ipamorelin and like other growth hormone releasing peptides (GHRPs, 1,2 and 6) it is a member of the ghrelin family of secretagogues. Similar to GHRP-6 and GHRP-2, it suppresses somatostatin and increases the stimulation of GHRH and thereby the release of hGH from the anterior pituitary.

Natural **peptides** typically have poor absorption, distribution, metabolism, and excretion (ADME) properties with rapid **clearance**, short **half-life**, and low permeability. The main causes of rapid **clearance of peptides** from **systemic** circulation **are** enzymatic proteolysis or/and **renal clearance**. Ipamorelin has a lower clearance than the other GHRP's providing it with greater exposure to tissues. Comparison of changes in plasma concentrations of the GHRP peptides following administration are shown below . As seen, ipamorelin showed a significantly lower systemic clearance when compared with the other peptides investigated[20].

This difference in systemic clearance was subsequently demonstrated to be reflected in the excretion profile as follows. GHRP-6 was predominantly excreted in the bile as the intact peptide. The biliary excretion was rapid with nearly half of the administered dose recovered after the first 30-minute sampling.

The excretion in urine, however, was much less, accounting for less than 10 percent of the administered dose. In contrast, urinary excretion was more important for ipamorelin clearance which was excreted mainly unchanged. This shows the resistance to enzymic attack and may contribute to the greater efficacy of ipamorelin.

Thus, Ipamorelin is a peptide hormone consisting of several unusual amino acids including, Aib-His-D-2-Nal-D-Phe-Lys-NH2, the combination of which contributes to its unique efficacy as a growth hormone secretagogue.

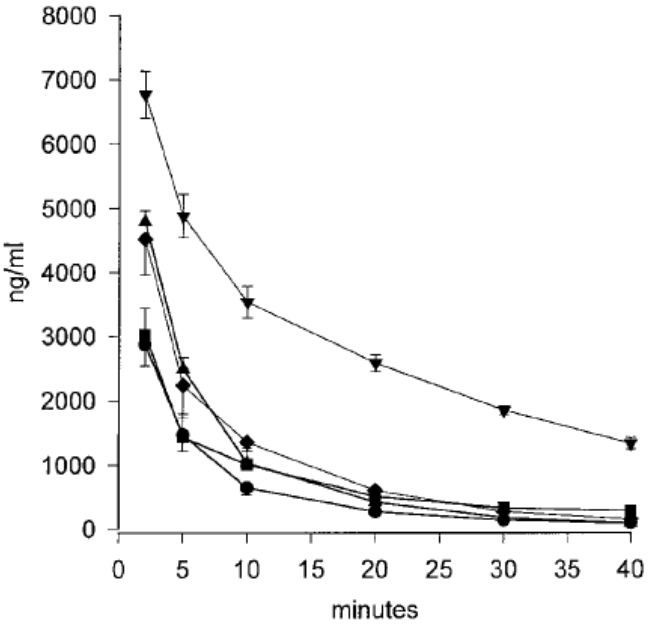



Figure 1. Plasma concentrations of different peptidyl GH secretagogues following single i.v. injections of 1 mg/kg to the male rat. Data are the means± SE of four to six animals. Ipamorelin (▼), GHRP-2 (▲), NNC 26-0235 (◆), GHRP-6 (■), NNC 26-0194 (●).

## Ipamorelin: "The other Sermorelin"

Ipamorelin is sometimes called the "other sermorelin" not because it is a member of the GHRH family of secretagogues, but rather because it shares the specificity of sermorelin for primarily stimulating hGH with minor effects on other hormones. Like pralmorelin (GHRP-2) and GHRP-6, ipamorelin does not affect prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), or thyroid-stimulating hormone (TSH) levels. However, unlike pralmorelin (GHRP-2) and GHRP-6, but similarly to growth hormone-releasing hormone (GHRH/sermorelin , ipamorelin also does not stimulate the secretion of adrenocorticotropic hormone (ACTH) or cortisol, and is highly selective for inducing the secretion of only GH. For this reason it was said to be "the first GHRP-receptor agonist with a selectivity for GH release similar to that displayed by GHRH/sermorelin"[17]. A comparison of the effects on GHRPs including ipamorelin versus sermorelin on the release of ACTH and cortisol is presented below. Note that while secondary hormone release by ipamorelin is slightly elevated, they are significantly lower than those produced by the other GHRPs and comparable to sermorelin.

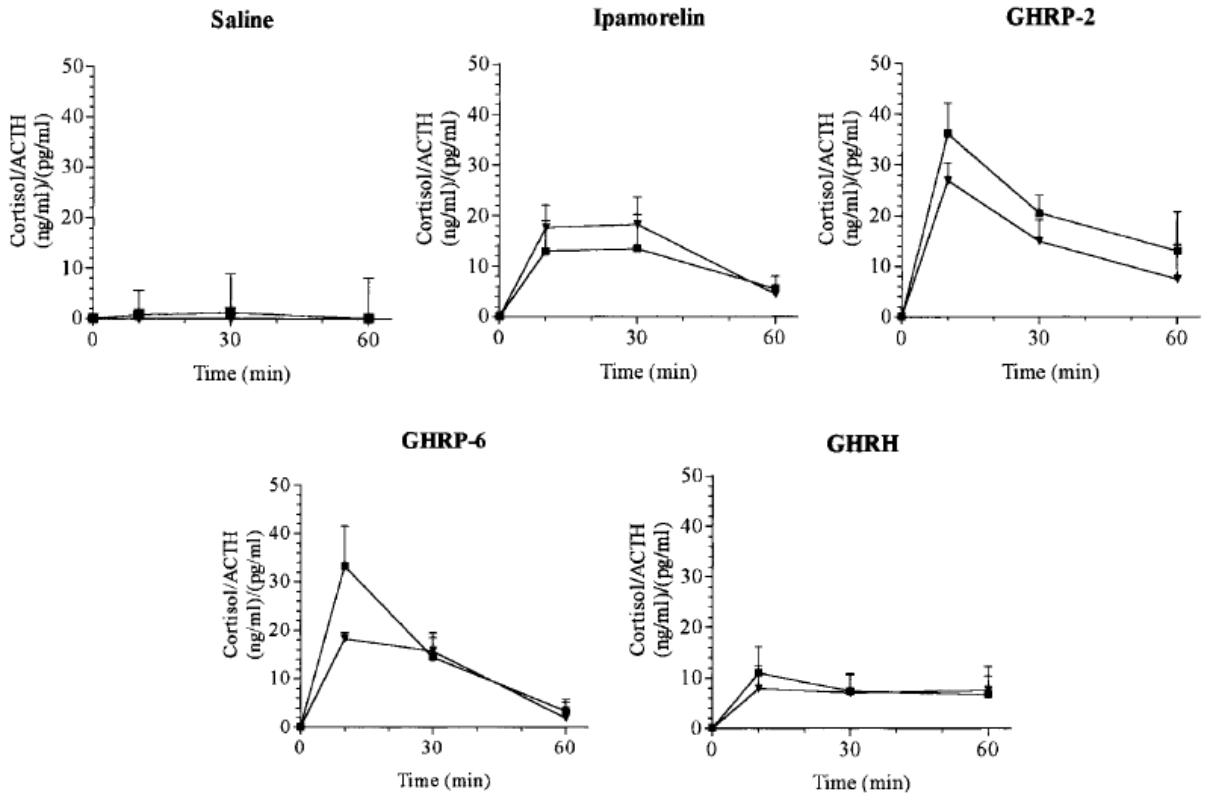



**Figure 3** Plasma ACTH (■) and cortisol (▼) levels versus time in swine following i.v. administration of saline, ipamorelin (210×GH $ED_{50}$ dose), GHRP-2 (45×GH $ED_{50}$ dose), GHRP-6 (85×GH $ED_{50}$ dose) and GHRH (200–300×GH $ED_{50}$ dose). Data, given as means±S.E.M., are from a single experiment carried out in six pigs and the individual basal hormone level is subtracted from the stimulated values. See Materials and methods for experimental details. $C_{max}$ values of ACTH and cortisol for GHRP-2 and GHRP-6 are significantly higher than those for ipamorelin and GHRH (*P<0.05, unpaired t*-test).

# Clinical Applications: Comments on Mono and Combined Therapies and Objectives

Individual or combined therapies are based upon the physician's interpretation of the patient's hormonal status, age, objective in treating, and many other aspects of consideration. It is because of this doctor's prerogative that we often refer to the "art of medicine" since treatments often reflect the skills and judgements of the physician in offering this/her patients the most effective treatments.

Generally speaking, however, sermorelin monotherapy is provided for relatively younger patients who have significant pituitary reserve and only need treatment for a few months, so as to increase exposure to endogenous hGH. Since sermorelin eventually down regulates its pituitary receptors and actually "turns off" production of endogenous GHRH due to ultra-short feedback and activation of somatostatin neurons in the hypothalamus, its efficacy of slowly lost and recovery is often required for restoration of function. In this sense, recovery may actually be facilitated by subsequent monotherapy with ipamorelin which will restore GHRH function and suppress somatostatin activity that is enhanced by sermorelin therapy.

Ipamorelin monotherapy is also beneficial when provocative testing reveals that pituitary reserve is low, possibly due to hypothalamic deficiency of GHRH and enhancement of somatostatin influence. This condition often occurs at early somatopause and can be treated well with ipamorelin alone. Finally, severe GHD that is relatively unresponsive to monotherapy of either peptide can be best treated by taking advantage of synergy between both families of peptides.

In this case, combinations of sermorelin and Ipamorelin in a ratio generally representing 2:1 (more or less) will be effective and most appropriate, especially for the older patient. Thus, because of the different properties of Ipamorelin and Sermorelin they are often used as monotherapies after identifying the condition to be best treated. However, under certain conditions of relatively severe growth hormone insufficiency, combination therapies are indicated.

**Studies Related to Ipamorelin**

Ipamorelin was a 3rd generation GHRP behind GHRP-6 and GHRP-2. originally developed by Novo Nordisk, was investigated in phase II clinical trials but subsequently was not deemed to be a commercially feasible product by the Company. Thereafter, it has been used in clinical settings where its popularity is growing either as a monotherapy or combined therapy with sermorelin.

Ipamorelin has been shown to be both highly potent and very selective in vivo and in vitro, and has also demonstrated good safety and tolerability in human clinical studies. As previously stated, research has shown that Ipamorelin is growth hormone specific which means that the pituitary hormones such as cortisol are unaffected. Increased cortisol can lead to enhanced lipogenesis (fat creation), visceral obesity (deep abdominal obesity), breakdown of tissues, and suppression of the immune system 21. Thus, ipamorelin does not have ghrelin's lipogenic properties and does not promote hunger. Consistent with this observation are several reports of ipamorelin being an effective approach for treating obesity. Besides its poor effect on releasing the lipogenic hormone cortisol, it is also more effective than other GHRPs in treating obesity because it is a much more stable form of ghrelin and has longer clearance time of several hours as compared with the classical GHRP's . This extended effect and lack of metabolic attack provides longer periods of efficacy while in the body. Importantly clearance of the ipamorealin in through the liver with little metabolic changes. This resistance to enzymatic degradation also increases it clinical utility. Since ipamorelin is relatively devoid of secondary effects on prolactin, ACTH and cortisol, which tend to increase fat and reduce muscle, the pentapeptide, perhaps in conjunction with sermorelin would be an effective approach to opposing obesity and excessive weight gain.

In one study, it was found that young female adults had increased bone mass due to 12 weeks of treatment with ipamorelin. This peptide compared to other GHRPs ensures the benefits without having to deal with possible negative side effects.

## Ipamorelin Side Effects

While few side effects have been reported, below are some that have been mentioned anecdotally. These if real, are undoubtedly related to excessive hGH exposure and thus, dosage should be reduced.

- Headache/light headedness
- Water retention
- Numbness in extremities
- Tiredness
- Decreased Insulin sensitivity
- Carpal tunnel symptoms

## Ipamorelin Positive Effects

In studies done on animal test subjects, Ipamorelin has been found to increase the amount of lean muscle with the development of new muscle cells. It has also shown to possibly have influence on the immune system. This positive effect is due to secondary actions of ghrelin on the body.

In a few studies, ipamorelin has also been found to increase the natural sleep patterns of test animals.

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