IPAMORELIN

Selective Growth Hormone Secretagogue | GHS-R1a Agonist | 3rd-Gen GHRP

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1. Peptide Description

- **Also known as:** NNC 26-0161 (Novo Nordisk investigational designation)
- **Peptide class:** GHRP / 3rd-generation ghrelin mimetic
- **Structure:** Synthetic pentapeptide (5 AA) — Aib-His-D-2-Nal-D-Phe-Lys-NH_2
- **FDA status:** Not approved — investigational compound
- **Generation rank:** Third-generation GHRP; most selective of the GHRP family
- **GH selectivity rank:** Highest in GHRP family — GHRH-like selectivity
- **Key structural feature:** D-amino acids + alpha-aminoisobutyric acid (Aib) confer protease resistance → ~2-hour half-life

2. Modes of Action & Mechanisms

GHS-R1a pathway — selective, pulsatile GH release

- Binds GHS-R1a (ghrelin receptor) on anterior pituitary somatotrophs with high affinity and superior selectivity vs. GHRP-2 and GHRP-6
- Direct somatotroph stimulation → GH exocytosis from secretory vesicles
- Hypothalamic activity: inhibits somatostatin's suppressive effect on GHRH release → removes GH brake upstream
- Does NOT stimulate ACTH, cortisol, prolactin, aldosterone, FSH, LH, or TSH — even at doses >200× the ED50 for GH
- Preserves normal pulsatile GH rhythm and intact somatostatin negative feedback — hypothalamic regulation not overridden

Intracellular signaling cascades

- Gq protein coupling → PLC activation → IP3 + DAG
  - IP3 mobilizes Ca^{2+} from endoplasmic reticulum; DAG activates PKC
  - Elevated intracellular Ca^{2+} triggers GH vesicle exocytosis from somatotrophs
- Concurrent cAMP/PKA cascade activation — amplifying second pathway
- EC50 = 1.3 nmol/L in vitro; ED50 = ~80 nmol/kg in vivo (vs. 115 nmol/kg for GHRP-6) — effective at lower concentrations than older GHRPs

Pulsatility and feedback preservation

- Single GH peak at ~40 min post-dose; exponential decline over 2–4 hours
- Physiological pulsatility maintained — no continuous supraphysiologic GH exposure
- Unlike exogenous GH: negative feedback via somatostatin is preserved → avoids chronic insulin resistance, receptor downregulation, and accelerated cellular senescence

NOTE: *Ipamorelin's defining advantage is what it does NOT do: no ACTH, no cortisol, no prolactin, no appetite surge — at any dose tested. This clean selectivity profile is the primary clinical differentiator from GHRP-2 and GHRP-6.*

3. Main Points of Clinical Relevance

1 Cleanest endocrine safety profile in the GHRP family

No ACTH, cortisol, or prolactin elevation — even at supraphysiologic doses. This makes ipamorelin appropriate for patients where HPA axis disruption, immune suppression, or hyperprolactinemia would be clinically significant. Adverse event rate in the Phase 2 trial was lower in the ipamorelin group (87.5%) than placebo (94.8%).

2 Physiologic GH restoration without the risks of exogenous GH

Pulsatile, feedback-regulated GH release avoids the pitfalls of continuous exogenous GH: no receptor downregulation, no chronic insulin antagonism, no loss of hypothalamic control. The preferred choice for age-related GH decline (somatopause) where restoring physiology — not supraphysiologic loading — is the goal.

3 Bone anabolism and counteraction of glucocorticoid-induced catabolism (preclinical)

Dose-dependent increases in longitudinal bone growth rate (42 → 52 μm/day, $p < 0.0001$) and bone mineral content in rats. In glucocorticoid-treated animals, periosteal bone formation rate increased 4-fold and GC-induced muscle weakness was counteracted. Suggests a potential adjunct role in steroid-induced osteoporosis and sarcopenia — human data pending.

4 GI prokinetic effects — potential GLP-1 adjunct

Ghrelin receptor-mediated cholinergic activation improves gastric emptying and colonic transit in preclinical models. A Phase 2 RCT in postoperative ileus showed a trend toward earlier meal tolerance (25.3 vs. 32.6 hrs) with a lower adverse event rate, though the primary endpoint was not met statistically. The prokinetic mechanism also positions ipamorelin as a potential candidate for managing GLP-1 agonist-induced gastroparesis.

5 Minimal glucose perturbation at therapeutic doses

Unlike GHRP-2 and exogenous GH, ipamorelin does not produce clinically significant glucose elevation at standard SC doses. GH-mediated transient insulin antagonism and mild hepatic gluconeogenesis are expected but modest. Over time, improved mitochondrial biogenesis and beta-oxidation enhance cellular glucose utilization. Still: stabilize poorly-controlled diabetics (often with GLP-1 agonists) before initiating any GH secretagogue.

6 Reduced receptor desensitization — allows multiple daily doses

Superior GHS-R1a affinity and selectivity mean ipamorelin drives less receptor involution than GHRP-2 or GHRP-6 at equivalent clinical doses. This allows once to three-times-daily dosing at 100 mcg without the same desensitization pressure seen with higher-dose GHRP-2 regimens. Still requires cycling to maintain receptor sensitivity.

7 Ideal anchor peptide for GHRH combination protocols

Combining ipamorelin (GHS-R1a agonism) with a GHRH analog (CJC-1295/MOD-GRF(1-29), sermorelin, tesamorelin) achieves dual receptor activation: amplified GH amplitude, synchronized pulsatile release within 30–40 min, and upstream somatostatin inhibition. Ipamorelin's clean profile makes it the safest GHRP choice in these combinations — particularly when cortisol and prolactin effects must be minimized.

4. Dosing Instructions & Delivery Options

Route	Dose	Frequency	Context / Notes
SC (preferred)	100–200 mcg	1–3× daily	Evening preferred; fasted state (30 min pre/90 min post meal); 29–31G insulin syringe
IV	0.03 mg/kg	BID × up to 7 days	Research / clinical trial use only; peak GH at ~40 min
Intranasal	~5× SC dose	2–3× daily	~20% bioavailability (preclinical rat data); not practical for routine clinical use
Oral	Not established	—	No viable route at present; rapid enzymatic degradation

Suggested titration framework

Phase	Dose / Timing	Notes
Weeks 1–2 (initiation)	100 mcg SC once daily; evening	Assess tolerance; establish fasted-state habit
Weeks 3–4 (escalation)	100 mcg once or twice daily	Check IGF-1 and fasting glucose; do not exceed 200 mcg per dose
Weeks 5–12 (maintenance)	100 mcg 1–3× daily	3-hr minimum between doses; align with nocturnal GH surge (bedtime) and/or post-exercise
Cycling	12 wks on / 4–6 wks off	No long-term human data beyond 7 days; cycling is mechanistically prudent

Key dosing principle: Stay at 100 mcg per dose (max 200 mcg). Ipamorelin's superior receptor affinity means you achieve comparable or greater GH release at lower doses than GHRP-2 or GHRP-6. Escalating dose does not proportionally increase GH output and accelerates receptor desensitization. Fasted-state timing and a 3-hr inter-dose window apply equally here. Note on CJC-1295 labeling: compounds dispensed by compounding pharmacies as "CJC-1295" are almost universally MOD-GRF(1-29) without DAC — half-life 10–15 min, not 3–5 days. Confirm with the dispensing pharmacy.

5. Evidence Profile

Evidence tier legend: ● *Human RCT / clinical trial* ○ *Animal / preclinical* ◎ *In vitro* ✕ *Critical gap* ~ *Theoretical*

- ● Dose-proportional PK confirmed in 40 healthy males (Phase 1, IV, 5 dose levels)*Human trial*
- ● Single GH peak at 0.67 hr; SC50 = 214 nmol/L; half-life ~2 hrs (IV data)*Human trial*
- ● No ACTH / cortisol / prolactin / FSH / LH / TSH stimulation at any dose tested*Human trial*
- ● Phase 2 RCT — postoperative ileus: favorable safety; AE rate lower than placebo; primary endpoint not met (NS)*Human trial*
- ○ Bone: dose-dependent longitudinal growth rate ↑, tibial/vertebral BMC ↑ (rats, 12 wks)*Animal only*
- ○ Glucocorticoid counteraction: periosteal formation rate ↑ 4×; muscle strength preserved (rats, 3 months)*Animal only*
- ○ GI prokinesis: gastric emptying normalized; colonic transit ↓; comparable to GHRP-6 at lower doses (rats)*Animal only*
- ○ GH-deficient mice: +15% body weight with ipamorelin vs. +95% with exogenous GH — physiologic vs. pharmacologic*Animal only*

✕ Human body composition / fat loss / sarcopenia outcomes *No data — critical gap*
✕ Long-term safety in humans (>7 days of controlled data) *No data*
✕ Combination RCTs with GHRH analogs (CJC-1295, sermorelin, tesamorelin) *Not completed*
~ Cancer risk with chronic IGF-1 stimulation *Theoretical only*

GHRP family comparison

Parameter	Ipamorelin	GHRP-2	GHRP-6	Hexarelin
GH potency	Moderate–High	Highest	High	High
Receptor selectivity	Highest	Moderate	Low	Moderate
Appetite stimulation	Minimal	Moderate	Strong	Minimal
Cortisol elevation	None	Mild	Significant	Mild
Prolactin elevation	None	Mild	Significant	Mild
Half-life	~2 hrs	~20–30 min	~20–30 min	~30 min
CD36 activity	Minimal	Mild–mod	Moderate	Strongest
Generation	3rd	2nd	1st	2nd

6. Clinical Considerations

Contraindications

- Active malignancy — GH/IGF-1 may promote tumor proliferation
- Uncontrolled diabetes mellitus — transient insulin antagonism; optimize metabolic health first
- Active pituitary tumors
- Pregnancy and lactation — no safety data
- Known hypersensitivity to GHRP-class peptides
- WADA-tested athletes — Class S2 prohibited substance

Monitoring protocol

- ***Baseline:*** IGF-1, fasting GH, fasting glucose, HbA1c, CMP, CBC, lipid panel, PSA (males >40)
- ***Week 4–6:*** IGF-1 (primary GH biomarker), fasting glucose, symptom review
- ***Week 12:*** Full panel + body composition (DEXA or InBody); cycle-off decision
- ***Annually:*** IGF-1, glucose, HbA1c, PSA, lipid panel, cancer screening per guidelines
- ***PRN:*** Signs of GH excess — peripheral edema, arthralgias, carpal tunnel, glucose intolerance
- Reduce or hold dose if IGF-1 exceeds upper limit of normal for age

No clinical guidelines exist — all monitoring is mechanistically derived.

Drug interactions & practical cautions

Interaction / Caution	Detail
Glucocorticoids	Ipamorelin may partially counteract steroid-induced bone and muscle catabolism — potentially beneficial, requires monitoring
GLP-1 receptor agonists	Ipamorelin's prokinetic GI effects may complement or correct GLP-1-induced gastroparesis — individualize

Interaction / Caution	Detail
Somatostatin analogs (octreotide)	Directly oppose GH release — avoid concurrent use
Insulin / antidiabetics	Monitor for glycemic changes; GH transiently antagonizes insulin action
Fasted-state timing	Carbs and fats blunt GH release — inject fasted; 30 min before eating or 90 min after
Carpal tunnel / edema	GH-mediated fluid retention — monitor for wrist pain and pitting edema; reduce or pause if needed
Injection site	Subcutaneous preferred; rotate sites; 29–31G syringe; 3-hr minimum between doses

Clinical bottom line: Ipamorelin is the right choice when the clinical priority is clean, physiologic GH restoration with the lowest hormonal footprint. Its defining strength — no ACTH, no cortisol, no prolactin at any tested dose — makes it uniquely suitable for patients where HPA axis integrity, metabolic stability, or concomitant corticosteroid use rule out GHRP-2 or GHRP-6. GH potency is moderate relative to GHRP-2 but more than sufficient for somatopause, recovery, and GH-axis support. Use it at 100 mcg, fasted, with a 3-hr inter-dose window, combine with a GHRH analog for synergistic effect, and cycle every 12 weeks. The absence of long-term human data is the central limitation — informed consent and structured monitoring are non-negotiable.

Final Note: Where Ipamorelin stands out vs. GHRP-2 and Hexarelin

Ipamorelin is the most selective and endocrinologically clean of the three — the right choice when avoiding cortisol, prolactin, or appetite effects is paramount. GHRP-2 is the more potent GH releaser and carries Japan-approved diagnostic use, making it preferable when maximum pulsatile GH amplitude is the goal (somatopause, sarcopenia, cachexia). Hexarelin has the strongest CD36/cardioprotective activity — it is the mechanistically superior choice for cardiac and anti-fibrotic applications, where GH release is secondary.

Ipamorelin's longer half-life (~2 hrs vs. 20–30 min for GHRP-2/Hexarelin) is a practical clinical advantage: a more forgiving dosing window, a less abrupt GH curve, and a more predictable pharmacokinetic profile. It also desensitizes the GHS-R1a more slowly, making it the preferred anchor in multi-dose or combination protocols.

The universal principle: lowest effective dose, strict cycling, fasted-state administration, and preference for GHRH analog combination over GHRP dose escalation — whether you are using ipamorelin, GHRP-2, or Hexarelin.