

RESEARCH MONOGRAPH · COMPOUND PROFILE

Ipamorelin

A 5-residue selective growth hormone secretagogue developed at Novo Nordisk in the late 1990s, characterized by GH release without coincident ACTH or prolactin stimulation.

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ABSTRACT

Ipamorelin (sequence Aib-His-D-2-Nal-D-Phe-Lys-NH₂; CAS 170851-70-4; molecular formula C₃₈H₄₉N₉O₅; molecular weight 711.86) is a synthetic pentapeptide growth hormone secretagogue (GHS) developed at Novo Nordisk in the mid-1990s and disclosed in a 1998 paper by Raun and colleagues. Ipamorelin is a selective agonist of the growth hormone secretagogue receptor 1a (GHS-R1a, the ghrelin receptor), the receptor through which the endogenous peptide ghrelin and the small-molecule MK-0677 also act. Selective activation of GHS-R1a triggers pulsatile growth hormone (GH) release from the anterior pituitary without the concurrent stimulation of cortisol, ACTH, or prolactin that complicates the pharmacology of older GHS compounds (GHRP-2, GHRP-6, hexarelin). The selectivity profile is the basis on which Ipamorelin remains the most-cited research-grade GHS in the post-2010 literature. The compound was advanced through Phase 2 trials by Helsinn Therapeutics for postoperative ileus before development was discontinued for commercial reasons. Reported preclinical activities include dose-dependent GH pulse induction, increased IGF-1 axis activity over multi-day administration, modest effects on appetite (smaller than ghrelin's), and accelerated bone mineral density gains in osteopenic rodent models. Plasma half-life is approximately 2 hours, with subcutaneous administration producing predictable absorption. The compound is not approved by any regulatory authority for human or veterinary use. The literature base is solid for the basic pharmacology but limited for long-term safety data in humans; the clinical record is principally from a single short-term ileus indication.

Compound identification

Nomenclature and synonyms

The most common designation is "Ipamorelin." The original developmental compound code at Novo Nordisk was NNC 26-0161. Less common synonyms include the chemical name 2-amino-N-((1R)-2-((2-((1R)-1-((1S)-(N-(5-amino-1-(carbamoyl)pentyl)imino)methyl)-2-naphthalenyl)methyl-1-oxoethyl)amino)-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl)-2-methylpropanamide. The CAS number is 170851-70-4. The PubChem CID is 9831659.

A point of nomenclature confusion is the GHRP family naming. Ipamorelin is sometimes lumped with GHRP-2, GHRP-6, hexarelin, and the small-molecule MK-0677 under the umbrella term "growth hormone-releasing peptides" (GHRPs). The structural and pharmacological boundaries are: GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂) and GHRP-2 (D-Ala-D-2-Nal-Ala-Trp-D-Phe-Lys-NH₂) are hexapeptides with documented prolactin and cortisol cross-stimulation. Ipamorelin is a pentapeptide with markedly improved selectivity. Hexarelin is a hexapeptide with the strongest GH effect but the most cortisol cross-stimulation. MK-0677 (ibutamoren) is a non-peptide small molecule with oral bioavailability and a long half-life; the pharmacokinetics differ substantially from the peptide GHSs.

Structural chemistry

The amino acid sequence is alpha-aminoisobutyric acid - L-histidine - D-2-naphthylalanine - D-phenylalanine - L-lysine - amide. The N-terminus carries the unnatural alpha-aminoisobutyric acid (Aib) residue, which provides metabolic stability against aminopeptidases. The presence of two D-amino acids (D-2-naphthylalanine at position 3 and D-phenylalanine at position 4) further enhances peptidase resistance and contributes to the receptor-binding pose. The C-terminus is amidated, increasing the peptide's lipophilicity and improving oral bioavailability relative to a free carboxylate, although Ipamorelin remains poorly bioavailable orally.

The molecular formula is C₃₈H₄₉N₉O₅; the average molecular weight is 711.86 g/mol; the monoisotopic mass is 711.39 daltons. The peptide has no disulfide bridges and no post-translational modifications. The free amine on the lysine side

chain provides the principal ionizable site at physiological pH, giving the peptide a net positive charge of +1 to +2 depending on the protonation state of the histidine imidazole.

Physicochemical properties

Ipamorelin is supplied as a white or off-white lyophilized powder. The lot of record (Kodiak biolabs lot 20260104) conforms to this description. Solubility in water and bacteriostatic water is high; concentrations up to 5 mg/mL are routinely prepared without precipitation. The peptide is also soluble in 0.9 percent saline, PBS, and standard biological buffers. Solubility in pure DMSO is poor; DMSO is not the appropriate vehicle for in vivo work.

The peptide is stable in the lyophilized state at minus 20 degrees Celsius for at least 24 months under the conditions documented in the lot expiration date. Reconstituted solutions in bacteriostatic water are stable for at least 30 days at 2 to 8 degrees Celsius; some published preparations have demonstrated stability up to 60 days under refrigeration. Freeze-thaw cycles should be avoided.

Discovery and developmental history

Origin in the Novo Nordisk GHS program

Ipamorelin emerged from a structure-activity relationship program at Novo Nordisk in the mid-1990s focused on improving the selectivity of growth hormone secretagogues. The parent structures (GHRP-6, GHRP-2, hexarelin) all stimulated GH release, but the cross-stimulation of cortisol, ACTH, and prolactin complicated their suitability as therapeutic candidates. The Novo Nordisk team systematically modified the hexapeptide template and identified Ipamorelin as the first pentapeptide GHS with clean selectivity for GH release.

The disclosure paper (Raun K, Hansen BS, Johansen NL, et al. European Journal of Endocrinology 139:552-561, 1998) reported that Ipamorelin produced a GH pulse comparable to GHRP-6 with no significant elevation of cortisol or prolactin at equipotent GH-releasing doses. This selectivity was confirmed in subsequent studies in rats, dogs, and humans.

Clinical translation

Helsinn Therapeutics licensed Ipamorelin and advanced it through Phase 2 trials in the early 2010s for postoperative ileus, the protracted slowing of gastrointestinal motility that follows abdominal surgery. The mechanism of action in this indication relates not to the GH-releasing activity but to the prokinetic effects mediated by ghrelin receptor activation in the enteric nervous system. The Phase 2 results were reported as encouraging but not definitive, with modest improvements in time-to-first-flatus and time-to-discharge endpoints. Helsinn discontinued development for commercial reasons rather than efficacy concerns.

There is no FDA-approved IND for Ipamorelin in any indication as of this revision. The compound is not a regulated drug substance in the United States, the European Union, or Japan. Clinical use in humans, where it occurs, is off-label and outside the scope of regulatory oversight.

Mechanism of action

GHS-R1a receptor agonism

The principal mechanism is selective agonism of the growth hormone secretagogue receptor 1a (GHS-R1a), a G-protein-coupled receptor expressed at high density in the anterior pituitary, the arcuate nucleus of the hypothalamus, and a subset of enteric neurons. Receptor activation triggers Gq-coupled phospholipase C signaling, IP3-mediated calcium release from intracellular stores, and protein kinase C activation in pituitary somatotrophs. The downstream consequence is exocytosis of stored growth hormone and the production of a pulsatile GH release pattern.

The selectivity for GH over ACTH, cortisol, and prolactin is mechanistically interesting because all four are anterior pituitary outputs. The selective profile reflects the absence of GHS-R1a expression on corticotrophs and lactotrophs and the absence of cross-activation of the receptors that drive ACTH and prolactin release at the doses required for GH stimulation. This is a structural property of the pentapeptide and not simply a dose-response artifact.

Synergy with GHRH

Ipamorelin and growth hormone-releasing hormone (GHRH) act on distinct receptors (GHS-R1a and GHRHR respectively) and trigger overlapping but non-redundant intracellular signaling. Co-administration of Ipamorelin with a GHRH analog (Sermorelin, CJC-1295 nDAC, Tesamorelin) produces a GH pulse substantially larger than either compound alone, on the order of 2 to 3 times the additive expectation. The synergy is the rationale for the most-cited research-grade GHS stack: Ipamorelin paired with CJC-1295 nDAC.

IGF-1 axis effects

Repeated GH pulsing over a multi-day timeframe drives systemic increases in insulin-like growth factor 1 (IGF-1) production from the liver. Plasma IGF-1 concentrations rise within the first week of regular Ipamorelin administration and continue to rise over the subsequent 4 to 8 weeks before reaching a new steady-state.

The IGF-1 axis effects are responsible for many of the indirect anabolic outcomes attributed to Ipamorelin (improved nitrogen retention, modest lean mass gains, accelerated bone mineral density gains) rather than direct effects of the peptide itself.

Appetite effects

Ghrelin, the endogenous GHS-R1a agonist, is a potent appetite stimulant. Ipamorelin has measurable but markedly weaker appetite-stimulating effects in published studies, in part because Ipamorelin does not cross the blood-brain barrier as efficiently as ghrelin and in part because the central appetite circuit involves additional ghrelin receptors and modulators not fully engaged by the synthetic pentapeptide. The practical consequence is that Ipamorelin is preferred over GHRP-6 and hexarelin in research contexts where appetite stimulation would confound the experimental endpoint.

Limits of the mechanistic model

The pharmacological mechanism is well characterized at the receptor and signaling level. The downstream physiological effects are well documented for GH and IGF-1 release. The longer-term consequences of repeated GHS-R1a stimulation are less well characterized; chronic ghrelin receptor activation in animal models has been associated with modest increases in adiposity in some preparations, although Ipamorelin's weaker appetite effects appear to mitigate this consequence relative to ghrelin or GHRP-6.

Pharmacokinetics

Routes of administration

Subcutaneous and intramuscular administration are the standard parenteral routes in published preclinical and clinical work. Both produce predictable absorption with peak plasma concentrations within 30 to 60 minutes. Oral bioavailability is poor (<5 percent) due to gastric and serum peptidase degradation. Intravenous administration produces the most rapid pharmacological effect but does not extend the duration of GH release; the GH pulse from a single Ipamorelin dose is over within 60 to 90 minutes regardless of route.

Plasma half-life

The plasma half-life is approximately 2 hours in humans and slightly shorter in rodents. The terminal elimination phase reflects peptidase clearance from circulation. The duration of the GH pulse triggered by Ipamorelin is shorter than the plasma half-life would suggest, because the somatotroph release is governed by receptor activation kinetics rather than peptide concentration alone.

Metabolism and excretion

Ipamorelin is hydrolyzed by serum peptidases at the C-terminal lysine and the central aromatic residues. The unnatural Aib at the N-terminus and the D-amino acids at positions 3 and 4 confer significant peptidase resistance relative to all-L peptides. Major metabolites are biologically inactive. Renal excretion of intact peptide and shorter fragments is the primary clearance route. The compound is not a known inducer or inhibitor of major CYP isoforms at expected exposure ranges.

Reported research dose ranges

The published preclinical literature reports rodent doses ranging from 10 to 200 micrograms per kilogram subcutaneously, with the bulk of pharmacology studies clustering around 30 to 100 micrograms per kilogram per dose. Allometric scaling to human equivalent doses places the equivalent human exposure in the range of 4 to 30 micrograms per kilogram per dose, or approximately 0.3 to 2.1 milligrams per dose for a 70 kg subject. Phase 2 clinical work in postoperative ileus used doses up to 0.07 milligrams per kilogram intravenously, broadly consistent with the upper end of the allometric range.

The dose range commonly cited in research-grade vendor literature (200 to 300 micrograms per research subject, two to three times daily, for 8 to 12 weeks) is somewhat higher than the allometrically scaled efficacy range but within the safety envelope established by the Phase 2 work. Pulsatile dosing (one to three pulses spaced through the day rather than continuous infusion) is preferred because GHS-R1a desensitizes under continuous stimulation; pulsatile dosing better mimics endogenous ghrelin physiology and avoids tachyphylaxis. Investigators should treat the published research-grade dose ranges as approximate guidance rather than validated dosing.

Sourcing and quality verification

Synthesis route

Ipamorelin is produced by solid-phase peptide synthesis using Fmoc chemistry. The synthesis is straightforward at small scale but presents two characteristic challenges: incorporation of the unnatural Aib residue at the N-terminus requires extended coupling times because Aib reacts more slowly than standard amino acids, and the D-amino acids at positions 3 and 4 require careful stereochemical control during coupling to avoid epimerization. C-terminal amidation is achieved by appropriate resin selection (Rink amide or similar).

The lot of record (Kodiak biolabs lot 20260104) was synthesized by the supplier of record and shipped in lyophilized acetate salt form. The vendor analytical report records 99.28 percent purity by HPLC (vendor COA value) with a supplementary HPLC report at 99.77 percent.

Common adulterants and impurities

The research-grade Ipamorelin supply chain has documented patterns of standard product. Reported issues include:

1. Substitution of Aib with alanine at the N-terminus, producing a peptide of correct length but reduced metabolic stability and altered receptor-binding kinetics. Mass spectrometry distinguishes the two readily (the alanine variant is approximately 14 daltons lighter).
2. Epimerization at the D-2-naphthylalanine or D-phenylalanine positions during prolonged synthesis, producing a peptide of correct mass but reduced GHS-R1a agonism. Chiral HPLC is required to detect this; standard reversed-phase HPLC does not separate the L/D variants reliably.
3. Deletion sequences from incomplete coupling, primarily at the N-terminal Aib position. These tetrapeptide impurities are biologically inactive.
4. Excess acetate or trifluoroacetate counterions inflating apparent mass by 5 to 12 percent depending on salt form.
5. Endotoxin contamination from non-pyrogen-controlled synthesis.

Independent verification by HPLC, mass spectrometry, and ideally chiral HPLC on every batch is essential. The vendor COA is necessary but not sufficient. Kodiak biolabs is in the process of establishing third-party verification through Janoshik Analytical; as of this revision only the vendor analytical report is available.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous TFA (0.1 percent) to acetonitrile, monitoring at 215 nm and 280 nm, is the standard purity assay. Identity confirmation by LC-MS yields a protonated molecular ion (M+H) at 712.4 m/z. The acceptance criteria applied by the vendor lab and replicated in the planned Janoshik verification are: total purity above 98.0 percent at both wavelengths, identity confirmation within 0.5 ppm of theoretical mass, and absence of major impurity peaks above 0.5 percent of the parent peak.

Reconstitution and handling

Solvent system

Ipamorelin dissolves readily in water, bacteriostatic water, and 0.9 percent saline. The standard reconstitution protocol uses bacteriostatic water (0.9 percent benzyl alcohol preservative) for any solution intended to be stored beyond a single use. For acute in vitro experiments where preservative is undesired, sterile water for injection or PBS works. DMSO is not the appropriate vehicle.

Reconstitution protocol

Add the calculated volume of solvent slowly along the side wall of the vial. A 5 mg vial reconstituted in 2 mL produces a 2.5 mg/mL solution; in 1 mL produces a 5 mg/mL solution. Allow the vial to rest at room temperature for 60 to 90 seconds, then gently swirl until the powder fully dissolves. The peptide is highly soluble; full dissolution is typically complete within 60 seconds. Visual inspection should confirm a clear solution without particulates.

Storage stability

Lyophilized Ipamorelin in the unopened vial: stable at minus 20 degrees Celsius for at least 24 months. Reconstituted solutions: stable at 2 to 8 degrees Celsius for at least 30 days, with extended stability up to 60 days under controlled refrigeration. Aliquot working solutions to avoid freeze-thaw cycles. Reconstituted solutions should not be stored at room temperature beyond 24 hours.

Stack interaction considerations

Combination with CJC-1295 nDAC (the unmodified GHRH analog without the drug affinity complex extension) is the most-cited research-grade GHS stack. The mechanistic basis is the synergy between GHS-R1a agonism and GHRH receptor agonism, which produces a GH pulse 2 to 3 times the additive expectation. The standard stack ratio in research-grade dosing is 100 micrograms each of Ipamorelin and CJC-1295 nDAC pulsed together, two to three times daily.

Combination with the long-acting CJC-1295 with DAC (drug affinity complex) extension produces sustained elevation of basal GH and IGF-1 rather than pulsatile stimulation. This stack is reported in research-grade literature but has a different physiological profile from the pulsatile Ipamorelin/CJC-1295 nDAC combination; sustained GH elevation has been associated with insulin sensitivity changes that pulsatile dosing largely avoids.

Combination with BPC-157 and TB-500 is reported on the rationale that GH receptor upregulation by BPC-157 may potentiate the anabolic effects of GH-axis stimulation, while TB-500 contributes connective tissue repair effects. The mechanistic case is plausible but not formally established in controlled comparison studies.

Pharmacokinetic interactions with CYP-substrate compounds are not expected at standard research dose ranges. Ipamorelin has no documented receptor-level interactions with conventional small-molecule pharmacotherapy.

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