MK-677

Ibutamoren Mesylate | Oral GHS-R1a Agonist | Non-Peptide Ghrelin Mimetic

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1. Peptide Description

- **Also known as:** Ibutamoren mesylate; MK-0677; NNC 26-0161 (original Merck designation)
- **Classification:** Non-peptide GHS-R1a agonist — ghrelin receptor mimetic (not a peptide)
- **Structure:** Small molecule (MW 528.7 g/mol); mimics N-terminal 4 residues of acylated ghrelin including octanoyl moiety
- **Route:** Oral — survives GI transit; not degraded by GI proteases unlike native ghrelin
- **Bioavailability:** >60% oral bioavailability
- **Half-life:** ~4.7 hours (plasma); functional GH elevation persists up to 24 hours
- **FDA status:** NOT approved — investigational only; Phase II completed; never reached Phase III
- **Development:** Developed by Merck; later licensed; being rebranded as LUM-201 for pediatric GH deficiency
- **Key comparator:** Anamorelin — FDA-approved in some countries for cancer cachexia; same receptor class, shorter GH response, longer half-life (~7–10 h)

2. Modes of Action & Mechanisms

GHS-R1a receptor activation — ghrelin mimicry

- Binds GHS-R1a (ghrelin receptor) in hypothalamus and anterior pituitary; mimics acylated ghrelin's critical N-terminal tetrapeptide and octanoyl moiety
- Stimulates GHRH release from hypothalamic neurons → amplifies GH production upstream
- Inhibits somatostatin tone → removes the GH brake
- Directly stimulates somatotroph GH secretion at the pituitary level
- GH pulse frequency increased dose-dependently; peak GH 55.9 mcg/L achieved at single dose
- IGF-1 cascade: GH acts on liver → IGF-1 synthesis; +40% at 8 weeks, +72.9% at 12 months (in clinical trials)

Intracellular signaling pathways

- **Gq/11 pathway (primary — GH release):** GHS-R1a activation → PLC-beta → IP3 release → intracellular Ca^{2+} surge → GH granule exocytosis; DAG → PKC activation → sustained response
- **Gi/o pathway (modulatory — somatostatin inhibition):** Gi/o activation → adenylyl cyclase inhibition → cAMP reduction → modulates SSTR signaling → disinhibition of GH secretion
- **Beta-arrestin recruitment:** Responsible for receptor desensitization (partial) — key reason for cycling requirements and dose discipline
- Cryo-EM structural confirmation (Liu 2021): binding pocket architecture of GHS-R1a with ibutamoren validated; confirms hydrophobic interactions critical for ghrelin mimicry

Pulsatility preservation and negative feedback

- Amplifies existing endogenous GH pulses — does not create continuous GH secretion
- Works through the intact hypothalamic-pituitary axis; somatostatin negative feedback remains active
- High IGF-1 blunts further stimulation — supraphysiologic exposure is self-limiting in a way exogenous GH is not
- Bedtime dosing aligns with nocturnal GH surge for additive physiologic effect

NOTE: *MK-677's critical advantage over exogenous GH: negative feedback is preserved. Exogenous rhGH bypasses the axis entirely — creating continuous supraphysiologic exposure, receptor downregulation, and chronic insulin antagonism. MK-677 amplifies the physiology; it does not replace it.*

3. Main Points of Clinical Relevance

1 Only oral GH secretagogue with sustained 24-hour GH elevation

MK-677's ~4.7-hour half-life and non-peptide structure make it unique among GH secretagogues: a single oral dose produces measurable GH elevation lasting up to 24 hours. No injection required. This is the defining practical advantage for patients who are injection-averse or require long-duration GH support. The sustained effect — not seen with any injectable GHRP — comes without sacrificing pulsatility, since amplification of existing pulses is the mechanism, not continuous secretion.

2 Robust, consistent IGF-1 elevation across diverse clinical populations

Six or more RCTs confirm reliable GHS-R1a target engagement: 25 mg/day restored IGF-1 to young-adult levels in healthy elderly (Chapman 1996); +40% IGF-1 in obese males at 8 weeks (Svensson 1998); +72.9% at 12 months in Alzheimer's patients (Sevigny 2008); +76% in hemodialysis patients (Campbell 2018). IGF-1 elevation is dose-dependent and sustained over 12+ months of therapy. This breadth of evidence across populations is unmatched by any injectable GHRP.

3 Lean mass preservation and anti-catabolic effect — confirmed in RCTs

The 12-month double-blind RCT (Nass 2008, n=65, age 60–81) showed FFM +1.1 kg vs. −0.5 kg placebo ($p<0.001$) and appendicular lean mass (TASM) +0.5 kg vs. −0.3 kg placebo. Crucially, no significant visceral fat change — a targeted lean mass gain. Anti-catabolic data (Murphy 1998) showed MK-677 fully reversed diet-induced negative nitrogen balance vs. placebo ($p<0.01$), confirming GH-driven protein anabolism and reduced catabolism. These are among the strongest body composition RCT results in the GHRP class.

4 Bone density synergy with bisphosphonates — mechanistically rational combination

Bisphosphonates (e.g., alendronate) block osteoclast-mediated bone resorption but do not stimulate bone formation. MK-677 adds the anabolic side: GH/IGF-1 axis activation drives osteoblast activity. Combined femoral neck BMD gain was +4.2% vs. +2.5% for alendronate alone at 12 months (Murphy 2001). Bone turnover markers confirmed: osteocalcin +15–29%, PICP +23%, IGFBP-5 +43–44%. This combination represents one of the best-characterized investigational uses of MK-677 — dual mechanism, clinical trial evidence.

5 ~50% increase in Stage IV sleep duration

MK-677 treatment increased Stage IV (deep/slow-wave) sleep by approximately 50% and REM sleep by >20% (Copinschi 1997). This is not a sedative effect — it reflects GH's physiologic role in sleep architecture, as the largest endogenous GH pulse occurs during Stage III/IV sleep. Improved sleep quality has downstream implications for recovery, cognitive function, and immune regulation, and is a clinically underappreciated benefit of GH-axis restoration.

6 Metabolic risk demands patient selection — glucose and insulin monitoring are non-negotiable

GH is a counter-regulatory hormone that transiently antagonizes insulin at the receptor level. MK-677-driven GH surges increase hepatic gluconeogenesis and impair oral glucose tolerance testing (observed at 2 and 8 weeks, Svensson 1998). HbA1c may rise with prolonged use, particularly at higher doses. This is the central metabolic risk. Stabilize pre-diabetic and T2DM patients — ideally with GLP-1

agonist therapy — before initiating any GH secretagogue. Over time, improved mitochondrial biogenesis and beta-oxidation can improve cellular glucose utilization, but this takes months.

7 CHF and edema — the reason Phase III never happened

Fluid retention is a known GH-class effect; MK-677's longer duration of GH elevation makes this more pronounced than with injectable GHRPs. The FDA flagged CHF risk and one trial was terminated early due to edema concerns — this is why MK-677 never advanced to Phase III. There was no cardiac injury data, but the hemodynamic risk in patients with pre-existing CHF, left ventricular dysfunction, or poorly controlled hypertension is real. The educator's solution: use 12.5 mg rather than 25 mg — near-maximal GH response with meaningfully less edema burden.

4. Dosing Instructions & Delivery Options

Route	Dose	Frequency	Context / Notes
Oral (only route)	12.5–25 mg	Once daily at bedtime	Aligns with nocturnal GH surge; 60%+ bioavailability; survives GI transit
Oral (advanced)	12.5 mg BID	Morning + bedtime	Exploits 4.7-hr half-life for dual pulsatile effect; lower edema risk per dose
Injectable	N/A	—	Not applicable — MK-677's unique value is oral bioavailability

Dose-response guide

Dose	GH / IGF-1 Effect	Tolerability	Clinical Notes
2–5 mg/day	Minimal–moderate IGF-1 rise; some GH pulse augmentation	Best tolerated	Sub-therapeutic for most indications; limited data
10 mg/day	Significant GH/IGF-1 stimulation; near-maximal GH response	Appetite begins	Favorable efficacy-to-side-effect ratio; educator's preferred starting point
12.5 mg/day	Near-maximal GH response	Moderate	Educator's preferred maintenance dose — strong effect, less edema than 25 mg
25 mg/day	Maximum studied dose; full IGF-1 restoration	Increased AEs	Phase II standard dose; higher edema and appetite risk; use cautiously in elderly

Suggested titration framework

Phase	Dose / Timing	Notes
Weeks 1–2 (initiation)	12.5 mg orally at bedtime	Assess tolerance; monitor fasting glucose and body weight at week 2
Weeks 3–8 (maintenance)	12.5 mg QHS or 12.5 mg BID (morning + bedtime)	Check IGF-1 and fasting glucose at week 4; assess for edema
Weeks 9–12 (evaluation)	Continue at effective dose; assess body composition	HbA1c, IGF-1, full metabolic panel; cycle-off decision

Phase	Dose / Timing	Notes
Cycling	12 weeks on / 4–6 weeks off	No long-term safety data; cycling reduces receptor desensitization risk

Key dosing principle: Start at 12.5 mg, not 25 mg. Near-maximal GH responses occur at 10–12.5 mg — the edema complications that derailed Phase III trials were dose-related. Bedtime administration is strongly preferred; it aligns with the physiological nocturnal GH surge and minimizes daytime appetite disruption. Do not escalate to 25 mg without confirming metabolic stability and absence of fluid retention at the lower dose. Cycling every 12 weeks is prudent given beta-arrestin-mediated receptor desensitization with prolonged use.

⚠ *MK-677 is not FDA-approved. No validated clinical dosing protocol exists. All dosing reflects investigational trial conditions and mechanistically derived educator frameworks only.*

5. Evidence Profile

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

◎ GHS-R1a binding mechanism confirmed by cryo-EM (Liu 2021) — binding pocket architecture validated*Structural / preclinical*

- ● GH pulse frequency increased dose-dependently; IGF-1 restored to young-adult levels in healthy elderly at 25 mg/day (Chapman 1996)*Human RCT*
- ● IGF-1 +40% in obese males at 8 weeks; FFM increased; impaired OGTT observed at 2 and 8 weeks (Svensson 1998)*Human RCT*
- ● Anti-catabolic: fully reversed diet-induced negative nitrogen balance vs. placebo ($p<0.01$); peak GH 55.9 mcg/L (Murphy 1998)*Human RCT*
- ● 12-month RCT: FFM +1.1 kg vs −0.5 kg placebo ($p<0.001$); TASM +0.5 kg; no visceral fat change (Nass 2008, n=65, age 60–81)*Human RCT*
- ● Bone: MK-677 + alendronate → femoral neck BMD +4.2% vs +2.5% alendronate alone; osteocalcin +15–29% (Murphy 2001)*Human RCT*
- ● Sleep: Stage IV sleep +~50%; REM sleep >+20% (Copinschi 1997)*Human RCT*
- ● Hemodialysis patients: IGF-1 +76% (1.76-fold); minimal AEs in renal population (Campbell 2018)*Human RCT*
- ● Alzheimer's: IGF-1 +72.9% at 12 months — robust target engagement confirmed; NO cognitive benefit on any endpoint (Sevigny 2008)*Negative RCT*

✕ Long-term safety (>24 months) — completely unestablished; no Phase III data*Critical gap*

✕ Hard clinical outcomes — fracture reduction, hospitalization, mortality, longevity — not studied*Critical gap*

✕ Cancer risk with prolonged GH/IGF-1 elevation — not studied in long-term trials*Critical gap*

✕ Head-to-head trials vs. approved GH therapies — not completed*Critical gap*

~ Combination with GHRH analogs or testosterone — mechanistically rational; no formal RCT data*Theoretical*

Comparison with GH secretagogues

Agent	Class / Route	Half-life	GH Response	FDA Status	Key Distinction
MK-677	Non-peptide / Oral	~4.7 h	High; up to 24 h elevation	Not approved	Only oral GH secretagogue;

Agent	Class / Route	Half-life	GH Response	FDA Status	Key Distinction
					longest sustained GH effect
Anamorelin	Non-peptide / Oral	~7–10 h	Moderate	Approved (cachexia, some countries)	Approved use; weaker GH/IGF-1 response than MK-677
GHRP-2	Peptide / SC	~20–30 min	Highest in GHRP class	Not approved	Most potent injectable GHRP; ACTH/cortisol elevation
GHRP-6	Peptide / SC	~15–60 min	High	Not approved	Strong appetite stimulation; significant cortisol effect
Ipamorelin	Peptide / SC	~2 h	Moderate–High	Not approved	Cleanest endocrine profile; no cortisol/ACTH
Sermorelin	GHRH analog / SC	~10–20 min	Moderate	Approved (pediatric)	Different mechanism (GHRH-R); FDA-approved

6. Clinical Considerations

Contraindications

- Active malignancy or history of GH-sensitive cancer — GH/IGF-1 may be pro-tumorigenic
- Congestive heart failure (CHF) or significant cardiac disease — FDA flagged; fluid retention may worsen LV function and elevate BP via renin-angiotensin system
- Uncontrolled diabetes mellitus — transient insulin antagonism; resolve metabolic issues first (GLP-1 agonists are the preferred bridge)
- Diabetic retinopathy — GH can worsen ocular complications of uncontrolled diabetes
- Acromegaly or documented GH excess
- Pregnancy or breastfeeding — no safety data
- Pediatric patients with open epiphyses — growth plate concerns, though not documented in trials

Patient selection criteria

- **Appropriate candidates (investigational only):** Age-related GH decline with functional sarcopenia; documented low IGF-1 with catabolic syndrome; osteoporosis refractory to standard therapy (combination with bisphosphonate); CKD-associated protein-energy wasting (pilot data)
- **High-risk / exclude:** Active or recent malignancy; CHF or significant cardiac disease; poorly controlled T2DM or pre-diabetes without metabolic optimization; acromegaly

Monitoring protocol

Timepoint	Labs / Assessments	Clinical Focus
Baseline	IGF-1, fasting glucose, HbA1c, fasting insulin, BMP, CBC, lipid panel, CMP, body weight; DEXA or InBody (optional)	Establish baseline; exclude contraindications

Timepoint	Labs / Assessments	Clinical Focus
Week 2	Fasting glucose, body weight, appetite and edema clinical assessment	Early glucose signal; tolerability check
Week 4	IGF-1, fasting glucose, HbA1c, body weight	Target engagement confirmation; glucose trend
Week 8	OGTT or fasting glucose, HbA1c, BMP, lipids, body weight, edema check	Detect insulin sensitivity changes
Month 3–6	IGF-1, fasting glucose, HbA1c, CMP, full metabolic panel, body composition (DEXA or InBody)	Sustained effect; intermediate body composition
Month 12	Full lab panel + DEXA + cardiac assessment if indicated	12-month efficacy and safety summary
Discontinuation	Wean vs. abrupt stop; IGF-1 may decline within days to weeks	Assess for rebound catabolism; reassess indication

No clinical guidelines exist — all monitoring is mechanistically derived from investigational trial conditions.

Drug interactions & practical cautions

Interaction / Caution	Detail
Bisphosphonates (alendronate)	Additive / synergistic for bone: anti-resorptive + anabolic — best-characterized combination; monitor bone turnover markers
GLP-1 receptor agonists	Metabolic bridge: optimize insulin sensitivity with GLP-1 before initiating MK-677; may run concurrently once metabolically stable
Insulin / antidiabetics	Monitor closely — GH transiently antagonizes insulin; glucose-lowering agents may need adjustment
Testosterone / HRT	Theoretically synergistic (dual anabolic pathways); no formal RCT data; monitor IGF-1 and metabolic panel
Somatostatin analogs (octreotide)	Directly oppose GH release — avoid concurrent use
Pre-existing CHF	Contraindicated — fluid retention may precipitate decompensation; renin-angiotensin activation; worsened hypertension
Edema / fluid retention	Monitor body weight weekly early; look for pitting edema, wrist pain, joint swelling — reduce or hold dose if present
Appetite stimulation	Expect increased caloric intake — beneficial if goal is lean mass; problematic if weight management is concurrent goal; timing bedtime dose limits daytime appetite surge

Clinical bottom line: MK-677 is the most evidence-supported oral GH secretagogue available, with 6+ RCTs confirming robust IGF-1 elevation, lean mass preservation, anti-catabolic effect, and bone synergy with bisphosphonates. Its oral route and 24-hour GH duration are unmatched in the class. The correct dose is 12.5 mg at bedtime — not 25 mg. The edema complications that ended Phase III were dose-dependent and patient-selection failures, not a fundamental flaw in the molecule. Use it at 12.5 mg in metabolically screened patients, cycle every 12 weeks, monitor glucose and fluid status from week 2, and combine with alendronate when bone

is the primary target. The absence of Phase III data and long-term safety characterization means informed consent and structured monitoring are mandatory — this is investigational medicine.

Final Note: Where MK-677 stands relative to injectable GHRPs and GHRH analogs

MK-677 occupies a unique pharmacological niche: the only oral, non-peptide option with sustained (24-hour) GH elevation and the deepest Phase II evidence base in the secretagogue class. It is not the most potent GH releaser per pulse — GHRP-2 holds that position — but it achieves sustained IGF-1 elevation that injectable GHRPs, with their 15–30 minute half-lives, simply cannot match with daily dosing.

Vs. injectable GHRPs: MK-677 wins on sustained IGF-1 elevation, oral convenience, body composition RCT depth, and bone evidence. The GHRPs win on pulse amplitude, flexibility of dosing frequency, and a cleaner edema profile (especially ipamorelin). MK-677's glucose and fluid effects require more vigilance than ipamorelin but are manageable with dose discipline.

Vs. GHRH analogs (sermorelin, tesamorelin, CJC-1295): MK-677 targets a different receptor (GHS-R1a vs. GHRH-R) and can theoretically be combined with GHRH analogs for dual-axis amplification — similar to the GHRP + GHRH rationale for injectable combinations. No formal RCT data exists for this combination, but the mechanistic logic is sound.

The universal principle: lowest effective dose (12.5 mg, not 25 mg), bedtime dosing, metabolic screening before initiation, cycle every 12 weeks, and structured monitoring from week 2 onward. MK-677 has earned its investigational use — it needs the dose discipline to keep it there.