Hormonaly ACADEMY

EVIDENCE MONOGRAPH · FOR LICENSED CLINICIANS

GLP-1 and Incretin Therapies

How they work, how to use them, and the law

A plain, evidence-graded guide to GLP-1 medicines: how they work, how to use them safely, what to expect when stopping or switching, what is coming next, and the rules on compounded and gray-market products.

First edition · 2026



GLP-1 · 7-36 amide HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

Fady Hannah-Shmouni, MD FRCPC
Endocrinologist and biochemical geneticist

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An evidence-based reference for licensed clinicians, with regulatory status verified through 11 November 2026. Educational content and a reference for clinical reasoning — not medical advice for any individual, and not a protocol for any unapproved use.

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How to use this book

How the chapters are built, what the evidence grades mean, and the limits of this reference.

HOW EACH CHAPTER IS BUILT

- A one-line statement of the clinical idea, then focused prose with inline citations [1].
- Evidence chips mark the kind of data behind a claim: human, regulatory, or mechanistic.
- A letter grade (A to D) rates the strength of evidence for the specific use described — not the elegance of the biology.
- KEY POINT boxes carry the practical takeaway; a References list closes each chapter.

WHAT THE GRADES MEAN

GRADE	MEANING
A	Consistent randomized trials or meta-analyses for the stated indication.
B	A single high-quality randomized trial, lower-quality trials, or strong observational data.
C	Limited data; mechanism plus small or uncontrolled studies.
D	Very low: preclinical, in vitro, or anecdotal only.

HOW TO USE THIS BOOK · CONTINUED

SCOPE AND A DISCLAIMER

Incretin-based therapies are approved for type 2 diabetes and, increasingly, for obesity and a widening set of cardiometabolic, renal and sleep indications, but they are also compounded, sold research-use-only, microdosed, stacked and used off-label on a large scale. This book states where the evidence is strong (weight reduction and glycemic control; cardiovascular, renal and sleep-apnea outcomes for specific agents), where it is weak or absent (microdosing, many off-label uses, most peptide stacking), and which agents and uses are investigational. Evidence grades reflect the clinical evidence for the specific indication discussed, not regulatory status or biological plausibility; a warm bar in the left margin marks contraindications, legal prohibitions and unapproved status. The book addresses adults; for pediatric indications (for example, Wegovy injection from age 12), consult the label.

This is educational content for licensed clinicians and a reference for clinical reasoning. It is not medical advice for any individual, does not establish a clinician-patient relationship, and does not replace specialist input or formal guidelines. Approvals, shortage and compounding status, and pipeline data change quickly and differ by country; statements here are dated to 2026. Verify current national sources, and confirm every citation and every dose against the primary literature and the current label before prescribing.

BEFORE YOU START

Keep three categories apart throughout: FDA-approved indications and doses (taken from the current label), off-label uses supported by trial evidence, and investigational or unapproved products. The book gives prescribing regimens only for approved uses. Study doses for off-label or investigational uses appear only where needed to describe the evidence and are identified as trial parameters, not dosing recommendations.

Incretin therapies at a glance

The monograph's core facts in brief.

FIELD	SUMMARY
Drug classes	GLP-1 receptor agonists (the peptide agents exenatide, lixisenatide, liraglutide, dulaglutide and semaglutide, and the oral nonpeptide agonist orforglipron); the dual GIP/GLP-1 agonist tirzepatide; and the investigational triple GIP/GLP-1/glucagon agonist retatrutide.
Main approved agents	Exenatide, liraglutide (including US generics), dulaglutide, semaglutide (subcutaneous; oral Rybelsus and Ozempic tablets, not mg-for-mg interchangeable, for type 2 diabetes; Wegovy injection and Wegovy 25 mg tablets for weight management), tirzepatide (Mounjaro, Zepbound), and oral orforglipron (Foundayo, approved April 2026).
Lead indications	Type 2 diabetes and chronic weight management. For specific agents, dated through November 2026: cardiovascular risk reduction (semaglutide SC and oral; liraglutide; dulaglutide; tirzepatide in type 2 diabetes, Mounjaro, August 2026), chronic kidney disease in type 2 diabetes (semaglutide SC, FLOW), moderate-to-severe obstructive sleep apnea in obesity (tirzepatide, Zepbound), and noncirrhotic MASH with F2 to F3 fibrosis (Wegovy injection, accelerated approval). Heart failure with preserved ejection fraction with obesity (STEP-HFpEF, SUMMIT), symptomatic peripheral artery disease in type 2 diabetes (STRIDE), and knee osteoarthritis in obesity (STEP 9; investigational retatrutide TRIUMPH-4) have positive phase 3 trial evidence but no standalone FDA indication.

INCRETIN THERAPIES AT A GLANCE · CONTINUED

FIELD	SUMMARY
Typical weight effect	Semaglutide 2.4 mg about 15% at 68 weeks (STEP 1); semaglutide 7.2 mg about 19% (STEP UP, intention-to-treat); oral semaglutide 25 mg about 14% at 64 weeks (OASIS 4); tirzepatide up to about 21% at 72 weeks (SURMOUNT-1); oral orforglipron about 11% at 72 weeks (ATTAIN-1); retatrutide up to 25.0% at 80 weeks in the phase 3 TRIUMPH-1 trial (treatment-regimen estimand; investigational). Figures are trial means, not label claims.
Dosing principle	Weekly or daily injection, or a daily oral tablet; titrate slowly for gastrointestinal tolerability. Oral semaglutide tablets must be taken fasting (empty stomach in the morning with up to 4 ounces of water, then at least 30 minutes before food); orforglipron may be taken at any time with or without food or water. For weight-management products, doses below the approved maintenance range are titration steps, not maintenance regimens; no approved microdosing regimen exists. Wegovy 1.7 mg is itself an approved maintenance dose, and Mounjaro 2.5 mg may remain an on-label T2D dose when additional glycemic control is not needed.
Key safety	Dose-dependent gastrointestinal effects; gallbladder disease; pancreatitis caution. Boxed thyroid C-cell tumor warning and MTC/MEN2 contraindication: liraglutide, dulaglutide, semaglutide, tirzepatide, orforglipron, and extended-release exenatide (Bydureon/Bydureon BCise); not short-acting exenatide (Byetta) or lixisenatide. Class-wide NAION warning (9 Nov 2026): seek urgent ophthalmic evaluation for sudden visual loss; if NAION develops, consider discontinuing the GLP-1 receptor agonist unless the treatment benefit clearly outweighs the risk. Watch for volume depletion and lean-mass/bone loss during rapid weight loss (pair with protein and resistance exercise). Perioperative management is risk-stratified rather than routine cessation.

INCRETIN THERAPIES AT A GLANCE · CONTINUED

FIELD	SUMMARY
Stopping therapy	Obesity is chronic and weight/cardiometabolic regain after discontinuation is common at the population level; stopping treatment also removes ongoing exposure to therapies with proven cardiovascular and renal benefits, and in large observational type 2 diabetes cohorts, treatment gaps are associated with higher MACE and all-cause mortality. When therapy is effective and tolerated, long-term maintenance is generally needed.
Regulation	Compounded and 'research-use-only' or 'not for human use' products are sold widely; research-use-only labeling does not make a product lawful for clinical use. The FDA resolved the tirzepatide and semaglutide injection shortages in 2024–2025, and the Fifth Circuit upheld those determinations in August 2026; verify current status against the FDA record.

Reading conventions: a warm bar in the left margin marks contraindications, prohibitions and statements that a product or use is not FDA-approved. Grades refer to the clinical evidence for the stated use.

H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R

PART 01

Foundations

The incretin hormones and their receptors, how GLP-1, GIP and glucagon act centrally and peripherally, the history from exendin-4 to the triple agonists, and the pharmacology of the approved agents.

IN THIS PART

The incretin system: GLP-1, GIP and glucagon

History and development of incretin therapies

Pharmacology of the approved agents

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