INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *GLP-1 Receptor Agonists Update*
-August 2026-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of glucagon-like peptide-1 receptor agonists (GLP-1) agents. Prior to this meeting, the IHS National Core Formulary (NCF) specified Ozempic® (semaglutide) for the treatment of diabetes and Wegovy® (semaglutide) or Zepbound® (tirzepatide) for chronic weight management. Following clinical review and analysis, the NPTC voted to **remove branded names** of Ozempic®, Wegovy® and Zepbound® and **added orforglipron** for chronic weight management with local criteria for use. Additionally**, language regarding tirzepatide and semaglutide was added** to include "when used for chronic weight management, recommend adoption of local use criteria".

Discussion:

GLP-1s (including dual agonists) have become first-line treatments for type II diabetes (T2DM), obesity, and many obesity related comorbidities. Spending in the United States (U.S.) on GLP-1s surpassed $71 billion in 2023; a more than 500% increase from $13.7 billion in 2018.[1] Approved indications for GLP-1s include T2DM, obesity, sleep apnea, chronic kidney disease, metabolic-associated steatohepatitis and cardiovascular disease. New molecules that act as dual and triple agonists (for the GLP-1, GIP, and glucagon receptors) are in clinical trials. U.S. Food and Drug Administration (FDA) approvals for GLP-1 products are affiliated with brand names, which are listed below as a visual organization tool.

Brand	Generic	Dosing	FDA approved indications
Ozempic®	Semaglutide	SC, weekly	(1) T2DM glycemic control (2) Reduction of MACE risk reduction in T2DM + CVD (3) Reduction of eGFR decline in T2DM + CKD
Rybelsus®	Semaglutide (oral)	Oral, daily	(1) T2DM glycemic control (2) Reduction of MACE risk reduction in T2DM + CVD
Wegovy® (SC)	Semaglutide	SC, weekly	(1) Chronic weight management (adults + pediatric ≥12 y) (2) Reduction of MACE risk reduction in CVD + obesity/overweight (3) Treatment of non-cirrhotic MASH with F2–F3 fibrosis
Wegovy® (oral)	Semaglutide (oral 25 mg)	Oral, daily	(1) Chronic weight management (adults) (2) Reduction of MACE risk in CVD + obesity/overweight
Mounjaro®	Tirzepatide (GIP/GLP-1)	SC, weekly	(1) T2DM glycemic control
Zepbound®	Tirzepatide (GIP/GLP-1)	SC, weekly	(1) Chronic weight management (adults, obesity/overweight + comorbidity) (2) Moderate-to-severe OSA in adults with obesity
Foundayo®	Orforglipron (oral, non-peptide)	Oral, daily	(1) Chronic weight management (adults, obesity/overweight + comorbidity)

T2DM = type II diabetes mellitus; MACE= major adverse cardiovascular events; CVD=cardiovascular disease; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; MASH=metabolic associated steatohepatitis; F2-F3 refers to fibrosis staging; mgmt.=management

New and emerging indications for GLPs: In August 2025, injectable Wegovy® acquired the indication for **treatment of MASH** based on data from the ESSENCE trials: phase 3 studies demonstrating resolution of steatohepatitis without worsening of fibrosis (62.9% semaglutide vs. 34.3% placebo (difference 28.7%; $p<0.001$)) and reduction in liver fibrosis (≥1 stage) without worsening of steatohepatitis (36.8% semaglutide vs. 22.4% placebo (difference 14.4%; $p<0.001$)).[9] Based on these results, injectable Wegovy® received accelerated FDA approval for noncirrhotic MASH with F2–F3 fibrosis, with continued approval contingent on long-term outcome data**. GLP-1 use in substance use disorder (SUD)** has also gained traction, although no FDA indication exists. GLP-1s modulate mesolimbic dopaminergic signaling in brain reward circuits, decreasing reward-driven behaviors in SUD. Observational data is promising: a Swedish nationwide cohort study (n=227,866 with AUD, median follow-up 8.8 years) found that semaglutide reduced alcohol use disorder (AUD) hospitalization risk by 36% (HR 0.64, 95% CI: 0.50-0.83) and liraglutide by 28% (HR 0.72, 95% CI: 0.57–0.92), outperforming approved AUD medications (naltrexone, disulfiram, acamprosate).[10] A U.S. Veterans Affairs (VA) cohort study (n=524,817) similarly found GLP-1 initiation was associated with an 18% lower risk of incident AUD compared with SGLT-2 inhibitors (HR 0.82, 95% CI: 0.78-0.85).[11] However, small RCTs have not shown benefit.[12] The same VA observational trial demonstrated GLP-1 use was associated with a 25% lower risk of incident opioid use disorder (HR 0.75, 95% CI: 0.67-0.85) and a 39% reduction in drug overdose among those with pre-existing SUD (HR 0.61, 95% CI: 0.42-0.88), lowered incident cannabis use disorder by 14% (HR 0.86, 95% CI: 0.81-0.90) and cocaine use disorder by 20% (HR 0.80, 95% CI: 0.72-0.88).[11] Heterogeneity and the observational bias of these studies necessitate further investigation. Use in **heart failure with preserved ejection fraction (HFpEF)** has been examined with semaglutide (STEP-HFpEF trial) and tirzepatide (SUMMIT trial) with inclusion criteria for both studies being BMI ≥30 with an ejection fraction (EF) ≥45% in STEP-HFpEF and ≥50% in SUMMIT.[13-14] The 2026 American College of Cardiology

Expert Consensus cites potential benefit from GLP-1s related to functional status and weight loss, without mortality benefit.[15] Concerns regarding sarcopenic obesity (low skeletal muscle mass with increased body fat) could pose a risk in older populations more commonly affected by HFpEF.[15] Lastly, use in neurodegenerative disorders (specifically, Parkinson's and Alzheimer's diseases) have not demonstrated benefit.[16-18]

Oral GLP1 review: **Semaglutide** (Wegovy® and Rybelsus®) has been studied and approved for treatment of obesity in the OASIS Program (3 industry funded RCTs) and T2DM in the PIONEER Program (13 industry funded RCTs). The PIONEER program included >9,500 patients demonstrating consistent, dose-dependent efficacy of oral semaglutide across the disease spectrum. Reductions in HbA1c ranged from −1.0% to −1.5% over 26-52 weeks, with oral semaglutide proving superior to placebo, empagliflozin, and sitagliptin, and noninferior to subcutaneous liraglutide 1.8mg, with 55-77% of patients achieving HbA1c <7.0% with the 14 mg dose.[19] The SOUL Trial examined the role of oral semaglutide in CVD and demonstrated a reduction of MACE by 14% (HR 0.86, 95% CI: 0.77-0.96; *p*=0.006), reduction in nonfatal MI (HR 0.74) and coronary revascularization (HR 0.75) with a number needed to treat of 50 to prevent one MACE event over 3 years (similar to injectable semaglutide).[20] The secondary endpoint (major kidney disease events) was *not significant* (HR 0.91, *p*=0.19).[20] Adherence in RCTs is high, however in real-world data, only ~50% of patients were able to tolerate the max dose (14mg) and 80% of patients experienced GI side effects.[19,21] Oral semaglutide must be taken according to the Core rule ("0-30-120"): one tablet, swallowed whole, first thing in the morning in a fasting state, with no more than 120 mL (≤4 oz) of plain water, then nothing by mouth (no food, other liquids, or other oral medications) for at least 30 minutes.[3]
Orforglipron (oral, non-peptide) was approved in 2026 by the FDA for chronic weight management in patients with obesity and overweight with weight associated comorbidities (comorbidities are not specified in the package insert).[8] Data for chronic weight management are confusing because doses used in the trials are NOT the available clinical doses, however the manufacturer has published dose equivalency for the capsules used in trials and the tablets that are commercially available.[22] The ATTAIN-1 study demonstrated clinically meaningful weight loss in obese patients without T2DM, specifically 55% of patients achieved ≥10%, 36% ≥15%, and 18% ≥20% weight loss with significant improvements in waist circumference, systolic blood pressure, triglycerides, and non-HDL cholesterol.[23] The ATTAIN-2 showed similar efficacy, but overall weight loss was lower in patients with T2DM.[22] In the ATTAIN-MAINTAIN trial, patients formerly controlled on semaglutide and tirzepatide were transitioned to orforglipron. While overall weight loss was greater with the injectable medications, patients taking orforglipron demonstrated weight maintenance: post-tirzepatide patients maintained weight 25.5% more vs. placebo (95% CI: 14.5-36.5; *p*<0.001) and post-semaglutide patients maintained weight loss 41.7% more vs. placebo (95% CI: 24.4-59.0; *p*<0.001).[24] In trials to demonstrate glycemic efficacy, the ACHIEVE trial program demonstrated non-inferiority to dapagliflozin (ACHIEVE-2), non-inferiority to oral semaglutide (ACHIEVE-3) and a meta-analysis across the program confirmed a 1.07% HbA1C reduction consistently across trials.[25,26]. A new drug application for orforglipron for the T2DM indication is expected in the near future.

Findings:

GLP-1 agents and their indications are rapidly expanding to treat a variety of disease states. Use of semaglutide for MASH addresses a growing health concern that directly affects the IHS service population and other indications are likely to be added in the future. Oral GLP-1 medications show promise in treatment of obesity and T2DM. Oral semaglutide has been shown to have benefits for CVD in patients with diabetes, but has practical challenges given the oral availability. Orforglipron has the data-backed indication for chronic weight management with promising trials supporting use in T2DM. Language regarding the use of branded products was removed from the NCF for ease of use in expanding indications and orforglipron was added as an oral alternative to the current injectable agents for practical ease of use and efficacy.

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