Front

Orfo™
(Orforglipron)
Tablet

اورفو

COMPOSITION:
Orfo Tablet 0.8 mg:
Each film coated tablet contains:
Orforglipron calcium 0.817 mg equivalent to
Orforglipron ..... 0.8 mg.

Product Specs.: Innovator

Orfo Tablet 2.5 mg:
Each film coated tablet contains:
Orforglipron calcium 2.554 mg equivalent to
Orforglipron ..... 2.5 mg.

Product Specs.: Innovator

Orfo Tablet 5.5 mg:
Each film coated tablet contains:
Orforglipron calcium 5.619 mg equivalent to
Orforglipron ..... 5.5 mg.

Product Specs.: Innovator

Orfo Tablet 9 mg:
Each film coated tablet contains:
Orforglipron calcium 9.194 mg equivalent to
Orforglipron ..... 9 mg.

Product Specs.: Innovator

Orfo Tablet 14.5 mg:
Each film coated tablet contains:
Orforglipron calcium 14.81 mg equivalent to
Orforglipron ..... 14.5 mg.

Product Specs.: Innovator

Orfo Tablet 17.2 mg:
Each film coated tablet contains:
Orforglipron calcium 17.57 mg equivalent to
Orforglipron ..... 17.2 mg.

Product Specs.: Innovator

CLINICAL PARTICULARS:
Therapeutic Indications:
Orforglipron is indicated, in combination with a reduced-calorie diet and increased physical activity, to reduce excess body weight and maintain weight reduction long term in:
- Adults with obesity
- Adults with overweight in the presence of at least one weight-related comorbid condition

Limitation of use: Concomitant use with another GLP-1 receptor agonist is not recommended.
Posology and Method of Administration:
Adults:
- **Starting dose:** 0.8 mg once daily
- After at least 30 days on 0.8 mg, increase to 2.5 mg once daily
- After at least 30 days on 2.5 mg, increase to 5.5 mg once daily
- The dose may then be increased to the next level (9 mg, 14.5 mg, or 17.2 mg once daily) after at least 30 days on the current dose, based on treatment response and tolerability
- **Maximum dose**: 17.2 mg once daily

The recommended starting dose and escalation schedule reduce the risk of gastrointestinal adverse reactions.
Missed Dose
• If a dose is missed, take it as soon as possible
• Do not double up the next dose
• If 7 or more consecutive doses are missed, dose escalation should be restarted at a lower dose to reduce the risk of gastrointestinal adverse reactions
Dose Modification with CYP3A4 Inhibitors and Inducers
• Strong CYP3A4 inhibitors: maximum dose is 9 mg once daily. Avoid strong CYP3A4 inhibitors that also inhibit OATP1B (e.g., ritonavir)
• Strong CYP3A4 inducers: avoid concomitant use
• Moderate CYP3A4 inducers: monitor effectiveness and escalate the dose as needed
Renal Impairment
• No dose adjustment is recommended, including in end-stage renal disease
Hepatic Impairment
• Mild or moderate (Child-Pugh A or B): no dose adjustment required
• Severe (Child-Pugh C): not recommended
Elderly
• No dose adjustment is required based on age
Pediatric Population
• Safety and effectiveness have not been established in patients under 18 years of age
Administration:
• Take orally once daily, at any time of day, with or without food
• Swallow tablets whole. Do not break, crush, or chew
• Do not take more than one tablet per day

Contraindications:
• Personal or family history of medullary thyroid carcinoma (MTC)
• Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
• Known serious hypersensitivity to orforglipron or any excipient (see section 6.1)

Special Warnings and Precautions for Use:
WARNING: RISK OF THYROID C-CELL TUMORS. Products with GLP-1 receptor agonist activity that are pharmacologically active in rats and mice have caused thyroid C-cell tumors in rodents. Orforglipron is not pharmacologically active in rats or mice and did not produce tumors in rodents; the human relevance of this class effect has not been determined. Patients should be counseled about the potential risk of MTC and the symptoms of thyroid tumors (a mass in the neck, difficulty swallowing, shortness of breath, persistent hoarseness). Routine monitoring of serum calcitonin or thyroid ultrasound is of uncertain value.
• Acute pancreatitis: Observe patients for persistent or severe abdominal pain (sometimes radiating to the back, with or without vomiting). If pancreatitis is suspected, discontinue treatment and initiate appropriate management

• Severe gastrointestinal reactions: Not recommended in patients with severe gastroparesis
• Acute kidney injury due to volume depletion: Monitor renal function in patients reporting nausea, vomiting, or diarrhea that could lead to dehydration, especially during initiation and dose escalation
• Hypoglycemia: Risk is increased when used with insulin or insulin secretagogues (e.g., sulfonylureas); a dose reduction of these medicines may be needed. Monitor blood glucose in patients with diabetes
• Hypersensitivity: Serious reactions (e.g., anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists. Discontinue and seek medical attention if suspected. Use caution in patients with prior anaphylaxis or angioedema with another GLP-1 receptor agonist
• Diabetic retinopathy: Monitor patients with a history of diabetic retinopathy for progression. Not studied in patients with retinopathy or macular edema requiring acute treatment
• Acute gallbladder disease: Cholelithiasis and cholecystitis have been reported. If cholecystitis is suspected, gallbladder studies and follow-up are indicated
• Pulmonary aspiration during anesthesia or deep sedation: Orforglipron delays gastric emptying. Patients should tell their healthcare providers before any planned surgery or procedure
• Heart rate: Mean heart rate increases of 4 to 5 beats per minute were observed; tachycardia was reported more often than with placebo
• Concomitant GLP-1 receptor agonists: Use with other GLP-1 receptor agonist medicines is not recommended

Interaction with Other Medicinal Products:
• Strong CYP3A4 inhibitors (e.g., clarithromycin) increase orforglipron exposure (AUC approximately 3.5-fold); maximum dose is 9 mg once daily
• Strong CYP3A4 inhibitors that also inhibit OATP1B (e.g., ritonavir) should be avoided
• Strong CYP3A4 inducers (e.g., carbamazepine) markedly reduce exposure (AUC approximately 82% lower) and should be avoided; moderate inducers (e.g., efavirenz) reduce exposure and may require dose escalation
• OATP1B inhibitors (e.g., cyclosporine) increased orforglipron AUC approximately 2.6-fold
• Simvastatin: orforglipron approximately doubles exposure to the active metabolite simvastatin acid; do not exceed simvastatin 20 mg once daily. No clinically relevant interaction was seen with atorvastatin or rosuvastatin
• Insulin and insulin secretagogues (e.g., sulfonylureas): increased risk of hypoglycemia; consider reducing their dose when starting orforglipron
• Oral hormonal contraceptives: delayed gastric emptying may affect absorption. Switch to a non-oral contraceptive method, or add a barrier method, for 30 days after starting and for 30 days after each dose escalation
• Other oral medicines: gastric emptying delay may affect their rate of absorption (acetaminophen Cmax decreased by 28% after the first 0.8 mg dose; the effect diminished with repeated dosing)
No effect on orforglipron exposure was seen with esomeprazole (acid-reducing agent). Orforglipron had minimal effect on midazolam (CYP3A4 substrate) and a small effect on digoxin (P-gp substrate; approximately 1.2-fold increase in exposure).

Fertility, Pregnancy and Lactation:
Pregnancy: Weight loss offers no benefit to a pregnant patient and may cause fetal harm. There are no adequate and well-controlled studies in pregnant women. When pregnancy is recognized, discontinue treatment. Women of childbearing potential should use effective contraception during treatment (see section 4.5 regarding oral contraceptives). A pregnancy exposure registry is available.
Lactation: Orforglipron was present in the milk of lactating rats. It is not known whether it is present in human milk. Not recommended during breastfeeding.
Fertility: No effects on male or female fertility were seen in rats at exposures well above the clinical exposure.
Effects on Ability to Drive and Use Machines

Back

The effect of orforglipron on the ability to drive and use machines has not been specifically studied. Dizziness and hypotension have been reported, and hypoglycemia may occur, particularly in combination with insulin or sulfonylureas. Patients should take care when driving or operating machinery if affected.

Undesirable Effects
Common (reported in 5% or more of patients; the highest frequencies were seen at higher doses and during dose escalation):
• Nausea (26–35%)
• Constipation (20–27%)
• Diarrhea (21–25%)
• Vomiting (13–24%)
• Dyspepsia (12–16%)
• Abdominal pain (13–14%)
• Headache (8–9%)
• Abdominal distension (7–9%)
• Fatigue (6–9%)
• Eructation (6–8%)
• Gastroesophageal reflux disease (6–7%)
• Flatulence (5–6%)
Hair loss was reported in 4–5% of patients and was associated with weight reduction (more frequent in women).
Other adverse reactions:
• Tachycardia (3%)
• Dizziness (4%)
• Hypotension (2%; more frequent with concomitant antihypertensive therapy)
• Hypoglycemia (particularly with sulfonylurea or insulin)
• Cholelithiasis (1%) and acute cholecystitis (0.4%)
• Dysgeusia (0.9%) and dysesthesia (up to 1%)
• Acute kidney injury (0.2%)
• Acute pancreatitis (uncommon)
Rare / postmarketing (reported with GLP-1 receptor agonists):
• Hypersensitivity reactions, including anaphylaxis and angioedema
• Hemorrhagic and necrotizing pancreatitis
• Ileus, intestinal obstruction, severe constipation including fecal impaction
• Acute renal failure or worsening of chronic renal failure
• Pulmonary aspiration during general anesthesia or deep sedation
Laboratory findings: mean increases in serum amylase (16–20%) and lipase (26–31%) were observed; their clinical significance is unknown in the absence of other signs of pancreatitis.
In clinical trials, 8% of patients discontinued treatment due to adverse reactions (versus 3% with placebo), mostly gastrointestinal. Most gastrointestinal reactions were mild to moderate and decreased over time.
Reporting of suspected adverse reactions: Patients and healthcare professionals are encouraged to report any suspected adverse reactions to the national reporting system.

Overdose:
In the event of overdose, contact a Poison Control Center or medical toxicologist. Initiate appropriate supportive treatment according to the patient's clinical signs and symptoms. A prolonged period of observation may be necessary, considering the long half-life of orforglipron.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Glucagon-like peptide-1 (GLP-1) receptor agonist (oral, non-peptide) | ATC code: to be confirmed
Orforglipron is a once-daily, small-molecule (non-peptide) oral agonist of the human glucagon-like peptide-1 (GLP-1) receptor.
Mechanism of Action
Orforglipron binds to and activates the human GLP-1 receptor. GLP-1 is a physiological regulator of appetite and caloric intake, and GLP-1 receptors are present in brain regions that regulate appetite. In animal studies, orforglipron distributed to and activated neurons in brain regions that regulate appetite and food intake.
Orforglipron is pharmacologically active at the human GLP-1 receptor but not in rats or mice.
Pharmacodynamic Effects
• Reduces body weight, with greater fat mass loss than lean mass loss
• Decreases food intake, likely mediated by decreased appetite
• Delays gastric emptying; the delay is largest after the first dose and diminishes over time
• Stimulates insulin release in the presence of elevated blood glucose
Cardiac Electrophysiology and QT Interval
At 1.4 times the mean maximum concentration provided by the maximum recommended dose (17.2 mg) once daily, clinically significant QTc interval prolongation was not observed.
Heart Rate and Blood Pressure
• Mean heart rate increased by approximately 3 to 5 beats per minute versus placebo
• Systolic blood pressure decreased by approximately 2.5 to 5 mmHg versus placebo
Clinical Efficacy
Efficacy was established in two 72-week, randomized, double-blind, placebo-controlled trials in adults aged 18 years and older, all with a reduced-calorie diet and physical activity counseling.
Trial 1 (ATTAIN-1; n = 3,127; obesity, or overweight with at least one comorbidity; without type 2 diabetes). Mean percent change in body weight at Week 72:
• Placebo: −2.1%
• 5.5 mg: −7.4%
• 9 mg: −8.3%
• 17.2 mg: −11.1%
Proportion achieving at least 5% weight loss: 26.8% (placebo) versus 59.6%, 63.1%, and 71.5% (5.5 mg, 9 mg, 17.2 mg).
Proportion achieving at least 10% weight loss: 13.0% versus 32.5%, 39.8%, and 54.5%.
Trial 2 (ATTAIN-2; n = 1,613; BMI of 27 kg/m² or more with type 2 diabetes). Mean percent change in body weight at Week 72:
• Placebo: −2.5%
• 5.5 mg: −5.1%
• 9 mg: −7.0%
• 17.2 mg: −9.6%
In patients with type 2 diabetes, HbA1c decreased by 1.2%, 1.4%, and 1.7% with 5.5 mg, 9 mg, and 17.2 mg, compared with 0.4% with placebo.
Reductions in waist circumference, non-HDL cholesterol, triglycerides, and systolic blood pressure were also observed. The results above are from the intent-to-treat (treatment-regimen) analysis.

Pharmacokinetic Properties
The pharmacokinetics of orforglipron is similar between healthy subjects and patients with overweight or obesity. Exposure increases in a dose-proportional manner. Steady state is reached after approximately 1 week of once-daily dosing.
Absorption
• Maximum plasma concentration is reached 4 to 8 hours after dosing
• Geometric mean absolute bioavailability: 77% (after a 0.8 mg dose)
• No clinically relevant food effect; the tablet can be taken with or without food, at any time of day
Distribution
• Mean steady-state volume of distribution: approximately 285 L (intravenous dosing)
• Plasma protein binding: greater than 99%
Metabolism
• Metabolized primarily by hepatic CYP3A4 to several oxidative metabolites, which are excreted into the intestinal lumen
• Also a substrate of CYP2J2
• Not a substrate of CYP1A2, 2B6, 2C8, 2C19, 2D6, or 3A5
• In vitro, does not inhibit or induce CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6
Elimination
• Mean systemic clearance: 7.15 L/hour
• Elimination half-life: approximately 29 to 49 hours
• After a single oral 2.5 mg dose, 87% of the dose was recovered in feces (all metabolites) and less than 1% in urine
Special Populations
Age, Sex, Race, Body Weight:
• No clinically relevant effect on pharmacokinetics (age 18–92 years; body weight 56.4–227 kg)
Renal Impairment:
• No change in pharmacokinetics, including in severe renal impairment and end-stage renal disease
Hepatic Impairment:
• Mild: exposure similar to normal hepatic function
• Moderate: AUC increased approximately 1.7-fold
• Severe: AUC increased approximately 4.6-fold (not recommended)
Transporter Interactions
Orforglipron is a substrate of P-glycoprotein, OATP1B1, and OATP1B3, and is not a substrate of BCRP or OCT1. It did not inhibit OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K in vitro.
Preclinical Safety Data
• Orforglipron was non-carcinogenic in a 2-year rat study and a 26-week transgenic mouse study. Because it is not pharmacologically active in rats or mice, the class-effect thyroid C-cell tumor findings seen with other GLP-1 receptor agonists could not be evaluated; their human relevance is unknown
• Not mutagenic or clastogenic in standard genotoxicity tests
• No effects on male or female fertility in rats
• In rabbits at high exposures (approximately 14 times clinical exposure), external malformations and decreased fetal weights were seen; no embryofetal effects were seen in monkeys at lower exposures.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Ofro Tablet 0.8 mg	:	Pack of 1 x 10 tablets.
Ofro Tablet 2.5 mg	:	Pack of 1 x 10 tablets.
Ofro Tablet 5.5 mg	:	Pack of 1 x 10 tablets.
Ofro Tablet 9 mg	:	Pack of 1 x 10 tablets.
Ofro Tablet 14.5 m	:	Pack of 1 x 10 tablets.
Ofro Tablet 17.2 mg	:	Pack of 1 x 10 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف معتمد ڈاکٹر کے نسخے پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

CCL
Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.
4862