OriYo

ORFORGLIPRON TABLET

0.8 mg | 2.5 mg | 5.5 mg | 9 mg | 14.5 mg | 17.2 mg

ORIYO (ORFORGLIPRON) TABLETS, FOR ORAL USE

National

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OriYo safely and effectively. See full prescribing information for OriYo.

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- In products with glucagon-like peptide-1 (GLP-1) receptor agonist activity that are pharmacologically active in rats and mice, rodent thyroid C-cell tumors (adenomas and carcinomas) have been observed at clinically relevant exposures and are considered GLP-1 receptor-dependent effects in rodents. Orforglipron is not pharmacologically active in rats or mice and did not produce tumors in rodents. While orforglipron is pharmacologically active at the human GLP-1 receptor, the human relevance of GLP-1 receptor-dependent thyroid C-cell tumors observed in rodents has not been determined (5.1).
- OriYo is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).

---------- INDICATIONS AND USAGE ----------

OriYo is a GLP-1 receptor agonist 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 or adults with overweight in the presence of at least one weight-related comorbid condition. (1)

Limitations of Use

Concomitant use with another GLP-1 receptor agonist is not recommended. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Take OriYo orally once daily, with or without food. (2.1)
- Swallow tablets whole. Do not break, crush, or chew. (2.1)
- Do not take more than one tablet per day. (2.1)
- Starting dosage is 0.8 mg once daily. After at least 30 days, increase dosage to 2.5 mg once daily. (2.1)
- After at least 30 days on the 2.5 mg dosage, increase dosage to 5.5 mg once daily. (2.1)
- Dosage may be increased to the next dosage level (9 mg, 14.5 mg, or 17.2 mg once daily) after at least 30 days on the current dosage, based on treatment response and tolerability. (2.1)
- Maximum dosage is 17.2 mg once daily. (2.1)

---------- DOSAGE FORMS AND STRENGTHS----------

Tablets: 0.8 mg, 2.5 mg, 5.5 mg, 9 mg, 14.5 mg, and 17.2 mg of orforglipron (3)

---------- CONTRAINDICATIONS ----------

- Personal or family history of MTC or in patients with MEN 2 (4)
- Known serious hypersensitivity to orforglipron or any of the excipients in OriYo (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Acute Pancreatitis: Has been observed in patients treated with GLP-1 receptor agonists, including OriYo. Discontinue if pancreatitis is suspected. (5.2)
- Severe Gastrointestinal Reactions: Use has been associated with gastrointestinal adverse reactions, sometimes severe. OriYo is not recommended in patients with severe gastroparesis. (5.3)
- Acute Kidney Injury Due to Volume Depletion: Monitor renal function in patients reporting adverse reactions that could lead to volume depletion. (5.4)
- Hypoglycemia: Concomitant use with insulin or an insulin secretagogue may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing the dosage of insulin or insulin secretagogue may be necessary. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. (5.5)
- Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists. If suspected, advise the patient to promptly seek medical attention and discontinue OriYo. (5.6)
- Diabetic Retinopathy Complications in Patients with Type 2 Diabetes: Has not been studied in patients with diabetic retinopathy and/or macular edema requiring acute treatment. Monitor patients with a history of diabetic retinopathy for progression. (5.7)
- Acute Gallbladder Disease: Has been reported in clinical trials. If cholecystitis is suspected, gallbladder studies and clinical follow-up are indicated. (5.8)
- Pulmonary Aspiration During General Anesthesia and Deep Sedation: Has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures. Instruct patients to inform healthcare providers of any planned surgeries or procedures. (5.9)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions, reported in ≥5% of patients treated with OriYo, are nausea, constipation, diarrhea, vomiting, dyspepsia, abdominal pain, headache, abdominal distension, fatigue, eructation, gastroesophageal reflux disease, flatulence, and hair loss. (6.1)

---------- DRUG INTERACTIONS ----------

- Strong CYP3A4 Inhibitors: The maximum dosage of OriYo is 9 mg once daily when used concomitantly with a strong CYP3A4 inhibitor. Avoid concomitant use with strong CYP3A4 inhibitors that also inhibit OATP1B. (7.1)
- CYP3A4 Inducers: Avoid concomitant use with strong CYP3A4 inducers. Monitor OriYo effectiveness and escalate dosage as needed when used concomitantly with moderate CYP3A4 inducers. (7.1)
- Simvastatin: Do not exceed simvastatin 20 mg once daily when used concomitantly with OriYo. (7.2)
- OriYo delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: May cause fetal harm. When pregnancy is recognized, discontinue OriYo. (8.1)
- Females of Reproductive Potential: Advise females using oral contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 30 days after initiation and for 30 days after each dose escalation. (8.3)
- Hepatic impairment: Not recommended for use in patients with severe hepatic impairment. (8.6)

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- In products with glucagon-like peptide-1 (GLP-1) receptor agonist activity that are pharmacologically active in rats and mice, rodent thyroid C-cell tumors (adenomas and carcinomas) have been observed at clinically relevant exposures and are considered GLP-1 receptor-dependent effects in rodents. Orforglipron is not pharmacologically active in rats or mice and did not produce tumors in rodents. While orforglipron is pharmacologically active at the human GLP-1 receptor, the human relevance of GLP-1 receptor-dependent thyroid C-cell tumors observed in rodents has not been determined [see Warnings and Precautions (5.1)].
- OriYo is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see Contraindications (4)]. Counsel patients regarding the potential risk for MTC with the use of OriYo and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with OriYo [see Contraindications (4), Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

OriYo 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 or adults with overweight in the presence of at least one weight-related comorbid condition.

Limitations of Use

Concomitant use with another GLP-1 receptor agonist is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

Recommended Administration

- Take OriYo orally once daily, with or without food.
- Swallow tablets whole. Do not break, crush, or chew.
- Do not take more than one tablet per day.

Recommended Dosage Escalation

Follow the OriYo starting dosage and escalation described below to reduce the risk of gastrointestinal (GI) adverse reactions [see Warnings and Precautions (5.3), Adverse Reactions (6)].

- The starting dosage is 0.8 mg orally once daily. After at least 30 days on the 0.8 mg dosage, increase the dosage to 2.5 mg once daily.
- After at least 30 days on the 2.5 mg dosage, increase the dosage to 5.5 mg once daily.
- The dosage may be increased to the next dosage level (9 mg, 14.5 mg, or 17.2 mg once daily) after at least 30 days on the current dosage, based on treatment response and tolerability.
- The maximum dosage of OriYo is 17.2 mg once daily.

2.2 Dosage Modification for Concomitant Use with CYP3A4 Inhibitors and CYP3A4 Inducers

OriYo dosage modification may be required to manage interactions with some concomitant medications [see Drug Interactions (7.1)].

Strong CYP3A4 Inhibitors

- Avoid strong CYP3A4 inhibitors that also inhibit OATP1B when taking OriYo.
- The maximum dosage of OriYo is 9 mg once daily when used concomitantly with a strong CYP3A4 inhibitor [see Drug Interactions (7.1)].

Strong and Moderate CYP3A4 Inducers

- Avoid strong CYP3A4 inducers when taking OriYo.
- Monitor OriYo effectiveness when concomitantly using moderate CYP3A4 inducers and escalate OriYo dosage as needed [see Dosage and Administration (2.1, 2.3), Drug Interactions (7.1)].

2.3 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to take the dose as soon as possible.
- Advise patients not to double up the next dose.
- If 7 or more consecutive doses are missed, reinitiate dosage escalation at a lower dosage to reduce the risk of gastrointestinal adverse reactions [see Dosage and Administration (2.1), Warnings and Precautions (5.3), Adverse Reactions (6)].

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 0.8 mg: pink, round, film-coated tablets without score.
- 2.5 mg: light yellow, round, film-coated tablets without score.
- 5.5 mg: grayish purple, round, film-coated tablets without score.
- 9 mg: pink, oval (caplet-shaped), film-coated tablets with a score on the upper punch.
- 14.5 mg: light yellow, oval (caplet-shaped), film-coated tablets with a score on the upper punch.
- 17.2 mg: grayish purple, oval (caplet-shaped), film-coated tablets with a score on the upper punch.

4 CONTRAINDICATIONS

OriYo is contraindicated in patients with:

- A personal or family history of MTC or in patients with MEN 2 [see Warnings and Precautions (5.1)].
- Known serious hypersensitivity to orforglipron or any of the excipients in OriYo. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 receptor agonists [see Warnings and Precautions (5.6), Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In products with GLP-1 receptor agonist activity that are pharmacologically active in rats and mice, rodent thyroid C-cell tumors (adenomas and carcinomas) have been observed at clinically relevant exposures and are considered GLP-1 receptor-dependent effects in rodents. Orforglipron is not pharmacologically active in rats or mice and did not produce tumors in rodents. While orforglipron is pharmacologically active at the human GLP-1 receptor, the human relevance of GLP-1 receptor-dependent thyroid C-cell tumors observed in rodents has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

OriYo is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of OriYo and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, or persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with OriYo. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Acute Pancreatitis

Acute pancreatitis has been reported in patients treated with OriYo. Fatal and non-fatal hemorrhagic or necrotizing pancreatitis have been observed in patients treated with GLP-1 receptor agonists [see Adverse Reactions (6)]. After initiation of OriYo, observe patients carefully for signs and symptoms of acute pancreatitis, which may include persistent or severe abdominal pain (sometimes radiating to the back) and which may or may not be accompanied by nausea or vomiting. If pancreatitis is suspected, discontinue OriYo and initiate appropriate management.

5.3 Severe Gastrointestinal Reactions

Use of OriYo has been associated with gastrointestinal adverse reactions, sometimes severe. In clinical trials, severe gastrointestinal adverse reactions were reported more frequently among patients treated with orforglipron (approximately 3%) than patients who received placebo (1%). Severe gastrointestinal adverse reactions have also been reported postmarketing with GLP-1 receptor agonists [see Adverse Reactions (6)].

OriYo is not recommended in patients with severe gastroparesis.

5.4 Acute Kidney Injury Due to Volume Depletion

There have been reports of acute kidney injury, in some cases requiring hemodialysis, in patients treated with GLP-1 receptor agonists or OriYo. The majority of the reported events occurred in patients who experienced gastrointestinal adverse reactions leading to dehydration such as nausea, vomiting, or diarrhea [see Adverse Reactions (6)]. Monitor renal function in patients reporting adverse reactions to OriYo that could lead to volume depletion, especially during dosage initiation and escalation of OriYo.

5.5 Hypoglycemia

OriYo lowers blood glucose and can cause hypoglycemia.

In a trial of adults with type 2 diabetes and BMI ≥27 kg/m^2 (Trial 2), hypoglycemia (plasma glucose <54 mg/dL) was reported in 2% of patients treated with orforglipron versus 0.2% of patients receiving placebo. One patient treated with orforglipron and no patients receiving placebo reported severe hypoglycemia in Trial 2. In Trial 2, 7% of patients treated with orforglipron once daily in combination with sulfonylurea reported hypoglycemia compared with 0.5% of patients not taking a sulfonylurea [see Adverse Reactions (6.1)]. There is also increased risk of hypoglycemia in patients treated with OriYo in combination with insulin [see Drug Interactions (7.2)]. Hypoglycemia has also been associated with OriYo and GLP-1 receptor agonists in adults without type 2 diabetes [see Adverse Reactions (6.1)].

Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In patients with diabetes, monitor blood glucose prior to starting OriYo and during OriYo treatment. The risk of hypoglycemia may be lowered by a reduction in the dose of insulin or sulfonylurea (or other concomitantly administered insulin secretagogue).

5.6 Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists [see Adverse Reactions (6.2)]. If hypersensitivity reactions occur, advise the patient to promptly seek medical attention and discontinue use of OriYo. OriYo is contraindicated in patients with a prior serious hypersensitivity reaction to orforglipron or to any of the excipients in OriYo. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with OriYo.

5.7 Diabetic Retinopathy Complications in Patients with Type 2 Diabetes

Temporary worsening of diabetic retinopathy has been reported with rapid improvement in glucose control. OriYo has not been studied in patients with diabetic retinopathy and/or macular edema requiring acute treatment. Monitor patients with a history of diabetic retinopathy for progression of diabetic retinopathy.

5.8 Acute Gallbladder Disease

Treatment with OriYo and GLP-1 receptor agonists is associated with an increased occurrence of acute gallbladder disease. In a pool of two clinical trials for weight reduction (Trials 1 and 2), cholelithiasis was reported in 1% of patients treated with orforglipron once daily and 0.7% of placebo-treated patients, and acute cholecystitis was reported in 0.4% of patients treated with orforglipron once daily and 0.3% of placebo-treated patients [see Adverse Reactions (6)]. Acute gallbladder events were associated with weight reduction. If cholecystitis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

5.9 Pulmonary Aspiration During General Anesthesia or Deep Sedation

OriYo delays gastric emptying. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking OriYo, including whether modifying preoperative fasting recommendations or temporarily discontinuing OriYo could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking OriYo.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-Cell Tumors [see Warnings and Precautions (5.1)]
- Acute Pancreatitis [see Warnings and Precautions (5.2)]
- Severe Gastrointestinal Reactions [see Warnings and Precautions (5.3)]
- Acute Kidney Injury Due to Volume Depletion [see Warnings and Precautions (5.4)]
- Hypoglycemia [see Warnings and Precautions (5.5)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.6)]
- Diabetic Retinopathy Complications in Patients with Type 2 Diabetes [see Warnings and Precautions (5.7)]
- Acute Gallbladder Disease [see Warnings and Precautions (5.8)]
- Pulmonary Aspiration During General Anesthesia or Deep Sedation [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in

OriYo

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ORIYO (ORFORGLIPRON) TABLETS, FOR ORAL USE

National

practice.

The safety of OriYo has been established 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 or adults with overweight in the presence of at least one weight-related comorbid condition based on adequate and well-controlled trials of an investigational orforglipron formulation (Trials 1 and 2), referred to in this section as OriYo. This section of labeling presents safety data from administration of the investigational orforglipron formulation shown as equivalent dosages of once daily OriYo [see Dosage and Administration (2.1)].

Adverse Reactions in Patients in Weight Management Clinical Trials

Pool of Two Placebo-Controlled Clinical Trials: OriYo was evaluated for safety in a pool of two randomized, double- blind, placebo-controlled trials that included 3155 adult patients with obesity or overweight treated with OriYo once daily for up to 72 weeks and a 2-week off-drug follow-up period (Trial 1 and Trial 2). The mean age of patients was 49 years and 41% were male. The population was 60% White, 25% Asian, 8% Black or African American, and 0.3% American Indian or Alaska Native; 35% identified as Hispanic or Latino ethnicity. At baseline, patients had an average BMI of 36.5 kg/m^2, 51% with a BMI ≥35 kg/m^2, 50% with hypertension, 49% with dyslipidemia, 31% with type 2 diabetes, 11% with obstructive sleep apnea, 3% with coronary artery disease, and 3% with cerebrovascular disease.

Across both trials, 8% of patients treated with OriYo (5.5 mg, 6%; 9 mg, 9%; and 17.2 mg, 10%) once daily permanently discontinued treatment as a result of adverse reactions compared to 3% of patients receiving placebo. The majority of patients (5%) who discontinued OriYo due to adverse reactions did so due to gastrointestinal adverse reactions.

Common Adverse Reactions

Table 1 shows common adverse reactions associated with the use of once daily OriYo in the pool of two placebo- controlled trials for weight management (Trials 1 and 2). These adverse reactions occurred more commonly with once daily OriYo than with placebo and occurred in at least 5% of patients treated with OriYo.

Table 1: Adverse Reactions Reported in ≥5% of OriYo-treated Adult Patients with Obesity or Overweight (With or Without Type 2 Diabetes) in Pool of Placebo-Controlled Trials (Trials 1 and 2)

Adverse Reaction	Placebo (N=1,576) %	OriYo 5.5 mg once daily (N=1,051) %	OriYo 9 mg once daily (N=1,055) %	OriYo 17.2 mg once daily (N=1,049) %
Nausea	10	26	34	35
Constipation	9	20	27	24
Diarrhea	11	21	23	25
Vomiting	4	13	21	24
Dyspepsia	4	12	16	13
Abdominal pain[a]	7	13	14	14
Headache	7	8	9	9
Abdominal distension	3	7	9	8
Fatigue[a]	4	6	7	9
Eructation	1	6	8	8
Gastroesophageal reflux disease	2	6	6	7
Flatulence	2	5	6	6
Hair loss[a]	2	4	4	5

[a] Includes other related terms.

Gastrointestinal Adverse Reactions

In a pool of Trials 1 and 2, gastrointestinal adverse reactions occurred more frequently among patients treated with once daily OriYo 5.5 mg (60%), 9 mg (68%), and 17.2 mg (69%) than placebo (37%). More patients treated with once daily OriYo 5.5 mg (3%), 9 mg (6%), and 17.2 mg (6%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.7%).

Of the OriYo-treated patients who reported GI adverse reactions, 60%, 36%, and 4% reported mild or moderate or severe adverse reactions, respectively. The incidence of nausea, vomiting, and diarrhea was higher during the OriYo dosage escalation period and decreased over time.

Hypoglycemia

In Trial 2, a trial of patients with type 2 diabetes and BMI ≥27 kg/m^2, hypoglycemia (glucose <54 mg/dL) was reported in 2% of OriYo-treated patients versus 0.2% of placebo-treated patients. One patient treated with OriYo 5.5 mg once daily, and no patients receiving placebo reported severe hypoglycemia in Trial 2. In this trial, 7% of patients taking OriYo in combination with sulfonylurea reported hypoglycemia compared with 0.5% of patients not taking sulfonylurea.

In Trial 1, a trial of OriYo in adults with BMI ≥27 kg/m^2 without type 2 diabetes, there was no systematic capturing of hypoglycemia, but glucose <54 mg/dL was reported in 0.6% of OriYo-treated patients and no placebo-treated patients. No patients in Trial 1 reported severe hypoglycemia.

Other Adverse Reactions

Acute Pancreatitis

In a pool of Trials 1 and 2, 6 events of acute pancreatitis were confirmed by adjudication in 6 OriYo-treated patients (0.14 patients per 100 years of exposure) versus 2 events in 1 placebo-treated patient (0.04 patients per 100 years of exposure).

Acute Kidney Injury

In a pool of Trials 1 and 2, acute kidney injury was reported in 0.2% of OriYo-treated patients compared to 0.05% of placebo-treated patients.

Hypotension

In a pool of Trials 1 and 2, hypotension occurred more frequently among patients taking OriYo (2%) than patients taking placebo (0.5%). Hypotension was more frequently seen in OriYo-treated patients on concomitant antihypertensive therapy (4%) compared to OriYo-treated patients not on antihypertensive therapy (1%).

Acute Gallbladder Disease

In a pool of Trials 1 and 2, cholelithiasis was reported in 1% of OriYo-treated patients and 0.7% of placebo-treated patients, and acute cholecystitis was reported in 0.4% of OriYo-treated patients and 0.3% of placebo-treated patients.

Tachycardia

In a pool of Trials 1 and 2, tachycardia (tachycardia, heart rate increased, and sinus tachycardia) was reported in 3% of patients treated with OriYo and 0.9% receiving placebo. Treatment with OriYo resulted in a mean increase in heart rate of 4 to 5 beats per minute from baseline compared to 0.5 beat per minute with placebo.

Hair Loss

Hair loss adverse reactions in OriYo-treated patients were associated with weight reduction. In a pool of Trials 1 and 2, hair loss was reported more frequently in female than male patients in the OriYo (7% female versus 0.9% male) and placebo (3% female versus 0.7% male) treatment groups.

Dizziness

In a pool of Trials 1 and 2, dizziness was reported in 4% of OriYo-treated patients and 3% of placebo-treated patients.

Dysgeusia

In a pool of Trials 1 and 2, dysgeusia was reported in 0.9% of OriYo-treated patients and 0.3% of placebo-treated patients.

Dysesthesia

In a pool of Trials 1 and 2, dysesthesia was reported in 0.3% and 1% of patients treated with OriYo 9 mg, and 17.2 mg, respectively, and 0.1% of patients receiving placebo. No patients taking OriYo 5.5 mg reported dysesthesia.

Hypersensitivity Reactions

In a pool of Trials 1 and 2, hypersensitivity reactions, including anaphylactic reaction, occurred in 0.5% of OriYo-treated patients compared to 0.3% of placebo-treated patients.

Laboratory Abnormalities

Amylase and Lipase Increase

In a pool of Trials 1 and 2, treatment with OriYo resulted in mean increases from baseline in serum pancreatic amylase concentrations of 16% to 20% and serum lipase concentrations of 26% to 31%, compared to mean increases from baseline in serum pancreatic amylase of 3% and serum lipase of 4% in placebo-treated patients. The clinical significance of elevations in amylase or lipase with OriYo is unknown in the absence of other signs and symptoms of pancreatitis.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of GLP-1 receptor agonists. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death; ileus, intestinal obstruction, severe constipation including fecal impaction

Hypersensitivity: anaphylaxis, angioedema

Pulmonary: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation

Renal and Urinary Disorders: acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on OriYo

Table 2 includes clinically relevant interactions where concomitant use of other drugs affects OriYo.

Table 2: Clinically Relevant Effects of Other Drugs on OriYo

Strong CYP3A4 Inhibitors	
Intervention	The maximum dosage of OriYo is 9 mg once daily when used concomitantly with a strong CYP3A4 inhibitor. Avoid concomitant use of OriYo with strong CYP3A4 inhibitors that also inhibit OATP1B (e.g., ritonavir) [see Dosage and Administration (2.2)].
Clinical Impact	CYP3A4 inhibitors increase OriYo exposure, which may increase the risk of OriYo-associated adverse reactions. Strong CYP3A4 inhibitors that also clinically inhibit OATP1B are expected to significantly increase plasma concentrations of OriYo, which may increase the risk of OriYo-associated adverse reactions [see Warnings and Precautions (5.3), Adverse Reactions (6.1)].
Strong CYP3A4 Inducers	
Intervention	Avoid concomitant use of OriYo with strong CYP3A4 inducers.
Clinical Impact	Induction of CYP3A4 decreases OriYo exposure, which may reduce the effectiveness of OriYo.
Moderate CYP3A4 Inducers	
Intervention	Monitor OriYo effectiveness and escalate dosage as needed when used concomitantly with moderate CYP3A4 inducers [see Dosage and Administration (2.1)].
Clinical Impact	Induction of CYP3A4 decreases OriYo exposure, which may reduce the effectiveness of OriYo.

7.2 Effect of OriYo on Other Drugs

Table 3 includes clinically relevant interactions where concomitant use of OriYo affects other drugs.

Table 3: Clinically Relevant Effects of OriYo on Other Drugs

Simvastatin	
Intervention	Do not exceed simvastatin 20 mg once daily when concomitantly used with OriYo.
Clinical Impact	Use of OriYo with simvastatin increased exposure of the active metabolite simvastatin acid two-fold. A two-fold increase in simvastatin acid exposure at the highest simvastatin dose could be clinically meaningful.
Insulin or Insulin Secretagogue (e.g., Sulfonylurea)	
Intervention	When initiating OriYo, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (e.g., sulfonylureas) [see Warnings and Precautions (5.5)].
Clinical Impact	OriYo stimulates insulin release in the presence of elevated blood glucose concentrations which could increase the risk for hypoglycemia when used in combination with insulin or insulin secretagogues.

7.3 Effect of OriYo on Oral Medications

OriYo delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications.

Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 30 days after initiation with OriYo and for 30 days after each dose escalation. Hormonal contraceptives that are not administered orally should not be affected.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OriYo (orforglipron) during pregnancy.

Risk Summary

Weight loss offers no benefit to a pregnant patient and may cause fetal harm. When a pregnancy is recognized, advise the pregnant patient of the risk to a fetus and discontinue OriYo.

There are no adequate and well-controlled studies of OriYo during pregnancy. Based on animal reproduction studies, there may be risks to the fetus from exposure to orforglipron during pregnancy.

Imbalances in malformations have been reported in rats and rabbits at low multiples of clinical exposure with GLP-1 receptor agonists active in those species. Orforglipron is not pharmacologically active in rats and rabbits.

In animal reproduction studies, oral administration of orforglipron to pregnant monkeys during organogenesis at doses lower than the maximum recommended human dose (MRHD) did not result in embryofetal effects. Higher dose levels and exposures could not be evaluated in monkeys due to dose limiting effects on body weight (see Data).

In a rabbit dose-range finding study, oral administration of orforglipron to pregnant rabbits during organogenesis at exposures 14 times the clinical exposure at the MRHD resulted in external malformations and decreases in fetal and placental weights in the absence of maternal toxicity (see Data). In the definitive rabbit study, oral administration of orforglipron to pregnant rabbits during organogenesis at exposures up to 6 times the clinical exposure at the MRHD did not result in embryofetal effects (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The estimated background risk of major birth defects and miscarriage for the indicated population is increased when compared to the general population.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Appropriate weight gain relative to pre-pregnancy weight is currently recommended for all pregnant patients, including those with obesity or overweight, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Animal Data

Embryofetal development was evaluated in pregnant monkeys administered orforglipron orally during organogenesis (gestation days 20 to 50) at doses of 0.15 and 0.7 mg/kg/day resulting in systemic exposures lower than the human exposure at the MRHD of 17.2 mg OriYo, based on AUC. No effects on pregnancy outcome, placental weight, fetal viability, fetal body weight, fetal measurements or external, visceral or skeletal evaluations were observed. Exposure in monkeys was lower than exposure at the MRHD. Higher dose levels and exposures cannot be achieved in pregnant monkeys due to on-target body weight effects.

Orforglipron is not pharmacologically active in rabbits. In a rabbit dose-range finding study, orforglipron was administered orally once daily during organogenesis (gestation days 7 to 19) at dose levels of 2, 20, and 200 mg/kg/day. These doses resulted in exposures that were approximately 0.03, 0.8 and 14 times, respectively, the clinical exposure at the MRHD, based on AUC. Statistically significant decreases in fetal and placental weights and external malformations in 2 fetuses from 2 dams were observed at 200 mg/kg/day. In the definitive rabbit study, orforglipron was given orally once daily during organogenesis (gestation days 7 to 19) at dose levels of 4, 40, and 200 mg/kg/day resulting in exposures approximately 0.06, 1.4, and 6.2 times the clinical exposure at the MRHD, respectively, based on AUC. No embryofetal effects were observed in the definitive rabbit study at any dose level.

Orforglipron is not pharmacologically active in rats. In a pre- and post-natal study in rats, orforglipron was administered orally once daily from implantation through lactation at doses of 5, 30, and 200 mg/kg/day, which resulted in exposures that were approximately 2.9, 4.5, and 13 times the clinical exposure at the MRHD, respectively, based on AUC. No effects were noted at any dose level in the F0 maternal rats or the F1 pups in the pre- and post-natal development study in rats.

In a tissue distribution study, [14C]orforglipron-derived radioactivity was not distributed to fetal tissues in pregnant rats.

8.2 Lactation

Risk Summary

There are no data on the presence of orforglipron or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Orforglipron was present in the milk of lactating rats in in vivo testing (see Data). When a drug is present in animal milk, it is likely that the drug will be present in human milk. OriYo is not recommended for nursing women. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OriYo and any potential adverse effects on the breastfed child from OriYo or from the underlying maternal condition.

Data

Animal Data: In a tissue distribution study, [14C]orforglipron-derived radioactivity was excreted into rat breast milk, with concentrations in milk 3-fold higher than in plasma.

8.3 Females and Males of Reproductive Potential

Contraception

Based on animal reproduction studies, there may be risks to the fetus from exposure to orforglipron during pregnancy [see Pregnancy (8.1)]. Advise women of childbearing potential to use effective contraception during treatment with OriYo. The effect of OriYo on the absorption of oral contraceptives has not been evaluated in a clinical trial. Because delayed gastric emptying may affect the absorption of oral medications, advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 30 days after initiation with OriYo and for 30 days after each dose escalation [see Drug Interactions (7.3)].

8.4 Pediatric Use

Safety and effectiveness of OriYo have not been established in pediatric patients.

8.5 Geriatric Use

In a pool of Trials 1 and 2, 399 (13%) OriYo-treated patients were 65 years of age or older, and 33 (1%) OriYo-treated patients were 75 years of age or older at baseline. No overall differences in safety or effectiveness of OriYo have been observed between patients 65 years of age or older and younger adult patients.

8.6 Hepatic Impairment

OriYo is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C).

No dosage modification of OriYo is recommended in patients with mild or moderate hepatic impairment (Child- Pugh Class A and B, respectively).

8.7 Renal Impairment

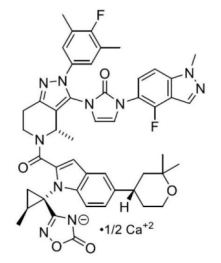
No dosage modification of OriYo is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in orforglipron pharmacokinetics (PK) was observed. Monitor renal function in patients reporting adverse reactions to OriYo that could lead to volume depletion [see Warnings and Precautions (5.4)].

9 OVERDOSAGE

In the event of an overdose, consider contacting a medical toxicologist for latest recommendations. Initiate appropriate supportive treatment according to the patient's clinical signs and symptoms. A period of observation and treatment for these symptoms may be necessary, considering the half-life of orforglipron.

10 DESCRIPTION

OriYo contains orforglipron, a GLP-1 receptor agonist. The molecular formula for orforglipron calcium is $C_{48}H_{47}F_2N_{10}O_5.[0.5]Ca$ and the molecular weight is 902.0 g/mol. The chemical name is calcium bis{3-[(1S,2S)-1-({2-(4- fluoro-3,5-dimethylphenyl)-3-({3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl]-4-methyl- 2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-yl}carbonyl)-5-[(4S)-2,2-dimethyloxan-4-yl]-1H-indol-1-yl}-2- methylcyclopropyl]-5-oxo-1,2,4-oxadiazol-4(5H)-ide}. Orforglipron calcium has the following chemical structure:



Orforglipron calcium is a white to practically white to light brown solid that is hygroscopic. Orforglipron calcium is insoluble in water.

OriYo tablets contain 0.8 mg, 2.5 mg, 5.5 mg, 9 mg, 14.5 mg or 17.2 mg of orforglipron (equivalent to 0.817 mg, 2.554 mg, 5.619 mg, 9.194 mg, 14.813 mg or 17.571 mg of orforglipron calcium, respectively) as film-coated tablets.

Each tablet contains 10 mg or less of sodium.

11 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

OriYo tablets are supplied as follows:

Strength	Tablet Description
0.8 mg	Pink, round, film-coated tablets without score
2.5 mg	Light yellow, round, film-coated tablets without score
5.5 mg	Grayish purple, round, film-coated tablets without score
9 mg	Pink, oval (caplet-shaped), film-coated tablets with a score on the upper punch
14.5 mg	Light yellow, oval (caplet-shaped), film-coated tablets with a score on the upper punch
17.2 mg	Grayish purple, oval (caplet-shaped), film-coated tablets with a score on the upper punch

30 tablets in one bottle.

Storage and Handling

Store at 20℃ to 25℃ (68℉ to 77℉); excursions permitted between 15℃ to 30℃ (59℉ to 86℉) [see USP Controlled Room Temperature].

OriYo is light sensitive. Protect from light by keeping in the original bottle and carton and replacing the cap each time after opening. If the carton is no longer available, store bottle away from light.

12 SHELF LIFE

2 years

13 MANUFACTURED AND MARKETED BY

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