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

OSENI (alogliptin and pioglitazone) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: CONGESTIVE HEART FAILURE
See full prescribing information for complete boxed warning
- **Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. (5.1)**
- **After initiation of OSENI and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in OSENI must be considered. (5.1)**
- **OSENI is not recommended in patients with symptomatic heart failure. (5.1)**
- **Initiation of OSENI in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. (4, 5.1)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions
Urinary Bladder Tumors (5.7) 12/2016
Bullous Pemphigoid (5.11) 12/2016

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

OSENI is a dipeptidyl peptidase-4 inhibitor and thiazolidinedione combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)

Important Limitations of Use: Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.1)

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

- Individualize the starting dose of OSENI based on the patient's current regimen and concurrent medical condition but do not exceed a daily dose of alogliptin 25 mg and pioglitazone 45 mg. (2.1)
- Can be taken with or without food. (2.1)
- Limit initial dose of pioglitazone to 15 mg once daily in patients with NYHA Class I or II heart failure. (2.1)
- Adjust dose if moderate renal impairment. (2.2)

Degree of Renal Impairment	Creatinine Clearance (mL/min)	Recommended Dosing
Moderate	≥30 to <60	12.5 mg/15 mg, 12.5 mg/30 mg or 12.5 mg/45 mg once daily

- OSENI is not recommended for patients with severe renal impairment or end-stage renal disease (ESRD) requiring dialysis. (2.2)
- The maximum recommended dose of pioglitazone is 15 mg once daily in patients taking strong CYP2C8 inhibitors (e.g., gemfibrozil). (2.3, 7.1)

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

Tablets:
25 mg alogliptin and 15 mg pioglitazone, 25 mg alogliptin and 30 mg pioglitazone, 25 mg alogliptin and 45 mg pioglitazone. (3)

12.5 mg alogliptin and 15 mg pioglitazone, 12.5 mg alogliptin and 30 mg pioglitazone, 12.5 mg alogliptin and 45 mg pioglitazone. (3)

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

- History of a serious hypersensitivity reaction to alogliptin or pioglitazone, components of OSENI, such as anaphylaxis, angioedema or severe cutaneous adverse reactions. (4)
- Do not initiate OSENI in patients with established NYHA Class III or IV heart failure. (4)

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

- Congestive heart failure: Fluid retention may occur and can exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk. Consider the risks and benefits of OSENI prior to initiating treatment in patients at risk for heart failure. Monitor patients at risk for heart failure for signs and symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of OSENI. (5.1)
- Acute pancreatitis: There have been postmarketing reports of acute pancreatitis. If pancreatitis is suspected, promptly discontinue OSENI. (5.2)
- Hypersensitivity: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin such as anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. In such cases, promptly discontinue OSENI, assess for other potential causes, institute appropriate monitoring and treatment and initiate alternative treatment for diabetes. (5.3)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt OSENI and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart OSENI if liver injury is confirmed and no alternative etiology can be found. Use with caution in patients with liver disease. (5.4)
- Edema: Dose-related edema may occur. (5.5)
- Fractures: Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health. (5.6)
- Bladder cancer: May increase the risk of bladder cancer. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer. (5.7)
- Hypoglycemia: When an insulin secretagogue (e.g., sulfonylurea) or insulin is used in combination with OSENI, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.8)
- Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes according to current standards of care with prompt evaluation for acute visual changes. (5.9)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate. (5.10)
- Bullous pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue OSENI. (5.11)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with OSENI. (5.12)

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

The most common adverse reactions (4% or greater incidence) are nasopharyngitis, back pain and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Strong CYP2C8 inhibitors (e.g., gemfibrozil) increase pioglitazone concentrations. Limit the pioglitazone dose to 15 mg daily. (2.3, 7.1)
- CYP2C8 inducers (e.g., rifampin) may decrease pioglitazone concentrations. (7.2)
- Topiramate may decrease pioglitazone concentrations. (7.3)

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

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE

- **Thiazolidinediones, including pioglitazone, which is a component of OSENI, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.1)]*.**
- **After initiation of OSENI and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in OSENI must be considered *[see Warnings and Precautions (5.1)]*.**
- **OSENI is not recommended in patients with symptomatic heart failure *[see Warnings and Precautions (5.1)]*.**
- **Initiation of OSENI in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

OSENI is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and pioglitazone is appropriate *[see Clinical Studies (14)].*

Important Limitations of Use

OSENI is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

OSENI should be taken once daily and can be taken with or without food. The tablets must not be split before swallowing.

The recommended starting dose for OSENI (alogliptin and pioglitazone):

- for patients inadequately controlled on diet and exercise is 25 mg/15 mg or 25 mg/30 mg,
- for patients inadequately controlled on metformin monotherapy is 25 mg/15 mg or 25 mg/30 mg,
- for patients on alogliptin who require additional glycemic control is 25 mg/15 mg or 25 mg/30 mg,
- for patients on pioglitazone who require additional glycemic control is 25 mg/15 mg, 25 mg/30 mg or 25 mg/45 mg as appropriate based upon current therapy,
- for patients switching from alogliptin coadministered with pioglitazone, OSENI may be initiated at the dose of alogliptin and pioglitazone based upon current therapy,
- for patients with congestive heart failure (NYHA Class I or II) is 25 mg/15 mg.

The OSENI dose can be titrated up to a maximum of 25 mg/45 mg once daily based on glycemic response as determined by hemoglobin A1c (A1C).

After initiation of OSENI or with dose increase, monitor patients carefully for adverse reactions related to fluid retention as has been seen with pioglitazone (e.g., weight gain, edema and signs and symptoms of congestive heart failure) *[see Boxed Warning and Warnings and Precautions (5.1)]*.

2.2 Patients with Renal Impairment

No dose adjustment of OSENI is necessary for patients with mild renal impairment (creatinine clearance [CrCl] ≥60 mL/min).

The dose of OSENI is 12.5 mg/15 mg, 12.5 mg/30 mg or 12.5 mg/45 mg once daily for patients with moderate renal impairment (CrCl ≥30 to <60 mL/min).

OSENI is not recommended for patients with severe renal impairment or ESRD *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Coadministration of pioglitazone and alogliptin 6.25 mg once daily based on individual requirements may be considered in these patients.

Because there is a need for dose adjustment based upon renal function, assessment of renal function is recommended prior to initiation of OSENI therapy and periodically thereafter.

2.3 Coadministration with Strong CYP2C8 Inhibitors

Coadministration of pioglitazone and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure approximately three-fold. Therefore, the maximum recommended dose of OSENI is 25 mg/15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].*

3 DOSAGE FORMS AND STRENGTHS

- 25 mg/15 mg tablets are yellow, round, biconvex, and film-coated, with both “A/P” and “25/15” printed on one side.
- 25 mg/30 mg tablets are peach, round, biconvex, and film-coated, with both “A/P” and “25/30” printed on one side.
- 25 mg/45 mg tablets are red, round, biconvex, and film-coated, with both “A/P” and “25/45” printed on one side.
- 12.5 mg/15 mg tablets are pale yellow, round, biconvex, and film-coated, with both “A/P” and “12.5/15” printed on one side.
- 12.5 mg/30 mg tablets are pale peach, round, biconvex, and film-coated, with both “A/P” and “12.5/30” printed on one side.
- 12.5 mg/45 mg tablets are pale red, round, biconvex, and film-coated, with both “A/P” and “12.5/45” printed on one side.

4 CONTRAINDICATIONS

History of a serious hypersensitivity reaction to alogliptin or pioglitazone, components of OSENI, such as anaphylaxis, angioedema or severe cutaneous adverse reactions.

Do not initiate in patients with NYHA Class III or IV heart failure *[see Boxed Warning]*.

5 WARNINGS AND PRECAUTIONS

5.1 Congestive Heart Failure

Consider the risks and benefits of OSENI prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of congestive heart failure. Patients should be advised of the characteristic symptoms of congestive heart failure and should be instructed to immediately report such symptoms**.** If congestive heart failure develops, it should be managed according to current standards of care and consider discontinuation of OSENI.

Alogliptin
In the EXAMINE trial which enrolled patients with type 2 diabetes and recent acute coronary syndrome, 106 (3.9%) of patients treated with alogliptin and 89 (3.3%) of patients treated with placebo were hospitalized for congestive heart failure.

Pioglitazone
Pioglitazone, like other thiazolidinediones, can cause dose-related fluid retention when used alone or in combination with other antidiabetic medications and is most common when pioglitazone is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure *[see Boxed Warning, Contraindications (4) and Adverse Reactions (6.1)]*.

5.2 Pancreatitis
Acute pancreatitis has been reported in the postmarketing setting and in randomized clinical trials. In glycemic control trials in patients with type 2 diabetes, acute pancreatitis was reported in six (0.2%) patients treated with alogliptin 25 mg and two (<0.1%) patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), acute pancreatitis was reported in ten (0.4%) patients treated with alogliptin and in seven (0.3%) patients treated with placebo.

It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using OSENI.

After initiation of OSENI, patients should be observed for signs and symptoms of pancreatitis. If pancreatitis is suspected, OSENI should promptly be discontinued and appropriate management should be initiated.

5.3 Hypersensitivity Reactions
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with alogliptin. These reactions include anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. If a serious hypersensitivity reaction is suspected, discontinue OSENI, assess for other potential causes for the event and institute alternative treatment for diabetes *[see Adverse Reactions (6.3)].* Use caution in patients with a history of angioedema with another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with OSENI.

5.4 Hepatic Effects
There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking pioglitazone or alogliptin, although some of the reports contain insufficient information necessary to establish the probable cause *[see Adverse Reactions (6.3)]*.

In glycemic control trials of alogliptin in patients with type 2 diabetes, serum alanine aminotransferase (ALT) elevations greater than three times the upper limit of normal (ULN) were reported in 1.3% of patients treated with alogliptin 25 mg and 1.7% of patients treated with active comparators or placebo. In the EXAMINE trial (a cardiovascular outcomes trial of patients with type 2 diabetes and high cardiovascular (CV) risk), increases in serum alanine aminotransferase three times the upper limit of the reference range occurred in 2.4% of patients treated with alogliptin and in 1.8% of patients treated with placebo.

Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel (ALT, aspartate aminotransferase [AST], alkaline phosphatase and total bilirubin) and assessing the patient is recommended before initiating OSENI therapy. In patients with abnormal liver tests, OSENI should be initiated with caution.

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