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

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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.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), OSENI treatment should be interrupted and an investigation done to establish the probable cause. OSENI should not be restarted in these patients without another explanation for the liver test abnormalities.

5.5 Edema

Pioglitazone

In controlled clinical trials, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose-related *[see Adverse Reactions (6.1)].* In postmarketing experience, reports of new onset or worsening of edema have been received.

OSENI should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, OSENI should be used with caution in patients at risk for congestive heart failure. Patients treated with OSENI should be monitored for signs and symptoms of congestive heart failure *[see Boxed Warning*, *Warnings and Precautions (5.1) and Patient Counseling Information (17)]*.

5.6 Fractures

Pioglitazone

In PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events), 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for pioglitazone versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and persisted during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in the incidence of fracture was observed in men treated with pioglitazone (1.7%) versus placebo (2.1%). The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care.

5.7 Urinary Bladder Tumors

Pioglitazone

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study *[see Nonclinical Toxicology (13.1)]*. In addition, during the three year PROactive clinical trial, 14 patients out of 2605 (0.54%) randomized to pioglitazone and 5 out of 2633 (0.19%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 6 (0.23%) cases on pioglitazone and two (0.08%) cases on placebo. After completion of the trial, a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROactive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR =1.00; [95% CI: 0.59–1.72]).

Findings regarding the risk of bladder cancer in patients exposed to pioglitazone vary among observational studies; some did not find an increased risk of bladder cancer associated with pioglitazone, while others did.

A large prospective10 year observational cohort study conducted in the United States found no statistically significant increase in the risk of bladder cancer in diabetic patients ever exposed to pioglitazone, compared to those never exposed to pioglitazone (HR =1.06 [95% CI 0.89–1.26]).

A retrospective cohort study conducted with data from the United Kingdom found a statistically significant association between ever exposure to pioglitazone and bladder cancer (HR: 1.63; [95% CI: 1.22–2.19]).

Associations between cumulative dose or cumulative duration of exposure to pioglitazone and bladder cancer were not detected in some studies including the 10 year observational study in the U.S., but were in others. Inconsistent findings and limitations inherent in these and other studies preclude conclusive interpretations of the observational data.

Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors.

Consequently, OSENI should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with OSENI should be considered in patients with a prior history of bladder cancer.

5.8 Use with Medications Known to Cause Hypoglycemia

Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycemia. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with OSENI.

5.9 Macular Edema

Pioglitazone

Macular edema has been reported in postmarketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but others were diagnosed on routine ophthalmologic examination.

Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione.

Patients with diabetes should have regular eye exams by an ophthalmologist according to current standards of care. Patients with diabetes who report any visual symptoms should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings *[see Adverse Reactions (6.1)].*

5.10 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.11 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving OSENI. If bullous pemphigoid is suspected, OSENI should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.12 Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with OSENI.

6 ADVERSE REACTIONS

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

- Congestive Heart Failure *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Hepatic Effects *[see Warnings and Precautions (5.4)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.10)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.11)]*

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 practice.

Alogliptin and Pioglitazone
Over 1500 patients with type 2 diabetes have received alogliptin coadministered with pioglitazone in four large, randomized, double-blind, controlled clinical trials. The mean exposure to OSENI was 29 weeks with more than 100 subjects treated for more than one year. The studies consisted of two placebo-controlled studies of 16 to 26 weeks in duration and two active-controlled studies of 26 weeks and 52 weeks in duration. In the OSENI arm, the mean duration of diabetes was approximately six years, the mean body mass index (BMI) was 31 kg/m^2 (54% of patients had a BMI ≥30 kg/m^2), and the mean age was 54 years (16% of patients ≥65 years of age).

In a pooled analysis of these four controlled clinical studies, the overall incidence of adverse reactions was 65% in patients treated with OSENI compared to 57% treated with placebo. Overall discontinuation of therapy due to adverse reactions was 2.5% with OSENI compared to 2.0% with placebo, 3.7% with pioglitazone or 1.3% with alogliptin.

Adverse reactions reported in ≥4% of patients treated with OSENI and more frequently than in patients who received alogliptin, pioglitazone or placebo are summarized in *Table 1*.

Table 1. Adverse Reactions Reported in ≥4% of Patients Treated with OSENI and More Frequently than in Patients Receiving Either Alogliptin, Pioglitazone or Placebo				
	Number of Patients (%)			
	OSENI*	**Alogliptin†**	**Pioglitazone‡**	**Placebo**
	N=1533	N=446	N=949	N=153
Nasopharyngitis	75 (4.9)	21 (4.7)	37 (3.9)	6 (3.9)
Back Pain	64 (4.2)	9 (2.0)	32 (3.4)	5 (3.3)
Upper Respiratory Tract Infection	63 (4.1)	19 (4.3)	26 (2.7)	5 (3.3)

*OSENI – includes data pooled for patients receiving alogliptin 25 mg and 12.5 mg combined with pioglitazone 15 mg, 30 mg and 45 mg
†Alogliptin – includes data pooled for patients receiving alogliptin 25 mg and 12.5 mg
‡Pioglitazone – includes data pooled for patients receiving pioglitazone 15 mg, 30 mg and 45 mg

Alogliptin Add-On Therapy to a Thiazolidinedione
In addition, in a 26 week, placebo-controlled, double-blind study, patients inadequately controlled on a thiazolidinedione alone or in combination with metformin or a sulfonylurea were treated with add-on alogliptin therapy or placebo; the adverse reactions reported in ≥5% of patients and more frequently than in patients who received placebo was influenza (alogliptin, 5.5%; placebo, 4.1%).

Hypoglycemia
In a 26 week, placebo-controlled factorial study with alogliptin in combination with pioglitazone on background therapy with metformin, the incidence of subjects reporting hypoglycemia was 0.8%, 0% and 3.8% for alogliptin 25 mg with pioglitazone 15 mg, 30 mg or 45 mg, respectively; 2.3% for alogliptin 25 mg; 4.7%, 0.8% and 0.8% for pioglitazone 15 mg, 30 mg or 45 mg, respectively; and 0.8% for placebo.

In a 26 week, active-controlled, double-blind study with alogliptin alone, pioglitazone alone or alogliptin coadministered with pioglitazone in patients inadequately controlled on diet and exercise, the incidence of hypoglycemia was 3% on alogliptin 25 mg with pioglitazone 30 mg, 0.6% on alogliptin 25 mg and 1.8% on pioglitazone 30 mg.

In a 52 week, active-controlled, double-blind study of alogliptin as add-on therapy to the combination of pioglitazone 30 mg and metformin compared to the titration of pioglitazone 30 mg to 45 mg and metformin, the incidence of subjects reporting hypoglycemia was 4.5% in the alogliptin 25 mg with pioglitazone 30 mg and metformin group versus 1.5% in the pioglitazone 45 mg and metformin group.

Alogliptin
A total of 14,778 patients with type 2 diabetes participated in 14 randomized, double-blind, controlled clinical trials of whom 9052 subjects were treated with alogliptin, 3469 subjects were treated with placebo and 2257 were treated with an active comparator. The mean duration of diabetes was seven years, the mean body mass index (BMI) was 31 kg/m^2 (49% of patients had a BMI ≥30 kg/m^2) and the mean age was 58 years (26% of patients ≥65 years of age).

The mean exposure to alogliptin was 49 weeks with 3348 subjects treated for more than one year.

In a pooled analysis of these 14 controlled clinical trials, the overall incidence of adverse reactions was 73% in patients treated with alogliptin 25 mg compared to 75% with placebo and 70% with active

comparator. Overall discontinuation of therapy due to adverse reactions was 6.8% with alogliptin 25 mg compared to 8.4% with placebo or 6.2% with active comparator.

Adverse reactions reported in ≥4% of patients treated with alogliptin 25 mg and more frequently than in patients who received placebo are summarized in *Table 2*.

Table 2. Adverse Reactions Reported in ≥4% Patients Treated with Alogliptin 25 mg and More Frequently than in Patients Given Placebo in Pooled Studies

	Number of Patients (%)		
	Alogliptin 25 mg	**Placebo**	**Active Comparator**
	N=6447	N=3469	N=2257
Nasopharyngitis	309 (4.8)	152 (4.4)	113 (5.0)
Upper Respiratory Tract Infection	287 (4.5)	121 (3.5)	113 (5.0)
Headache	278 (4.3)	101 (2.9)	121 (5.4)

Hypoglycemia

Hypoglycemic events were documented based upon a blood glucose value and/or clinical signs and symptoms of hypoglycemia.

In the monotherapy study, the incidence of hypoglycemia was 1.5% in patients treated with alogliptin compared to 1.6% with placebo. The use of alogliptin as add-on therapy to glyburide or insulin did not increase the incidence of hypoglycemia compared to placebo. In a monotherapy study comparing alogliptin to a sulfonylurea in elderly patients, the incidence of hypoglycemia was 5.4% with alogliptin compared to 26% with glipizide.

In the EXAMINE trial, the incidence of investigator reported hypoglycemia was 6.7% in patients receiving alogliptin and 6.5% in patients receiving placebo. Serious adverse reactions of hypoglycemia were reported in 0.8% of patients treated with alogliptin and in 0.6% of patients treated with placebo.

Renal Impairment

In glycemic control trials in patients with type 2 diabetes, 3.4% of patients treated with alogliptin and 1.3% of patients treated with placebo had renal function adverse reactions. The most commonly reported adverse reactions were renal impairment (0.5% for alogliptin and 0.1% for active comparators or placebo), decreased creatinine clearance (1.6% for alogliptin and 0.5% for active comparators or placebo) and increased blood creatinine (0.5% for alogliptin and 0.3% for active comparators or placebo) *[see Use in Specific Populations (8.6)]*.

In the EXAMINE trial of high CV risk type 2 diabetes patients, 23% of patients treated with alogliptin and 21% of patients treated with placebo had an investigator reported renal impairment adverse reaction. The most commonly reported adverse reactions were renal impairment (7.7% for alogliptin and 6.7% for placebo), decreased glomerular filtration rate (4.9% for alogliptin and 4.3% for placebo) and decreased renal clearance (2.2% for alogliptin and 1.8% for placebo). Laboratory measures of renal function were also assessed. Estimated glomerular filtration rate decreased by 25% or more in 21.1% of patients treated with alogliptin and 18.7% of patients treated with placebo. Worsening of chronic kidney disease stage was seen in 16.8% of patients treated with alogliptin and in 15.5% of patients treated with placebo.

Pioglitazone
Over 8500 patients with type 2 diabetes have been treated with pioglitazone in randomized, double-blind, controlled clinical trials, including 2605 patients with type 2 diabetes and macrovascular disease treated with pioglitazone in the PROactive clinical trial. In these trials, over 6000 patients have been treated with pioglitazone for six months or longer, over 4500 patients have been treated with pioglitazone for one year or longer, and over 3000 patients have been treated with pioglitazone for at least two years.

Common Adverse Reactions: 16 to 26 Week Monotherapy Trials
A summary of the incidence and type of common adverse reactions reported in three pooled 16 to 26 week placebo-controlled monotherapy trials of pioglitazone is provided in *Table 3*. Terms that are reported represent those that occurred at an incidence of >5% and more commonly in patients treated with pioglitazone than in patients who received placebo. None of these adverse reactions were related to pioglitazone dose.

Table 3. Three Pooled 16 to 26 Week Placebo-Controlled Clinical Trials of Pioglitazone Monotherapy: Adverse Reactions Reported at an Incidence >5% and More Commonly in Patients Treated with Pioglitazone than in Patients Treated with Placebo

	% of Patients	
	Placebo N=259	**Pioglitazone** N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Pharyngitis	0.8	5.1

Congestive Heart Failure
A summary of the incidence of adverse reactions related to congestive heart failure for the 16 to 24 week add-on to sulfonylurea trials, for the 16 to 24 week add-on to insulin trials, and for the 16 to 24 week add-on to metformin trials were (at least one congestive heart failure, 0.2% to 1.7%; hospitalized due to congestive heart failure, 0.2% to 0.9%). None of the reactions were fatal.

Patients with type 2 diabetes and NYHA class II or early class III congestive heart failure were randomized to receive 24 weeks of double-blind treatment with either pioglitazone at daily doses of 30 mg to 45 mg (N=262) or glyburide at daily doses of 10 mg to 15 mg (N=256). A summary of the incidence of adverse reactions related to congestive heart failure reported in this study is provided in *Table 4*.

Table 4. Treatment-Emergent Adverse Reactions of Congestive Heart Failure (CHF) in Patients with NYHA Class II or III Congestive Heart Failure Treated with Pioglitazone or Glyburide		
	Number (%) of Subjects	
	Pioglitazone N=262	**Glyburide** N=256
Death due to cardiovascular causes (adjudicated)	5 (1.9%)	6 (2.3%)
Overnight hospitalization for worsening CHF (adjudicated)	26 (9.9%)	12 (4.7%)
Emergency room visit for CHF (adjudicated)	4 (1.5%)	3 (1.2%)
Patients experiencing CHF progression during study	35 (13.4%)	21 (8.2%)

Congestive heart failure events leading to hospitalization that occurred during the PROactive trial are summarized in *Table 5*.

Table 5. Treatment-Emergent Adverse Reactions of Congestive Heart Failure (CHF) in PROactive Trial		
	Number (%) of Patients	
	Placebo N=2633	**Pioglitazone** N=2605
At least one hospitalized congestive heart failure event	108 (4.1%)	149 (5.7%)
Fatal	22 (0.8%)	25 (1%)
Hospitalized, nonfatal	86 (3.3%)	124 (4.7%)

Cardiovascular Safety

In the PROactive trial, 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. Almost all patients (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrates, diuretics, aspirin, statins and fibrates). At baseline, patients had a mean age of 62 years, mean duration of diabetes of 9.5 years and mean A1C of 8.1%. Mean duration of follow-up was 34.5 months.

The primary objective of this trial was to examine the effect of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in a cardiovascular composite endpoint that included all-cause mortality, nonfatal myocardial infarction (MI) including silent MI, stroke, acute coronary syndrome, cardiac intervention including coronary artery bypass grafting or percutaneous intervention, major leg amputation above the ankle

and bypass surgery or revascularization in the leg. A total of 514 (19.7%) patients treated with pioglitazone and 572 (21.7%) placebo-treated patients experienced at least one event from the primary composite endpoint (hazard ratio 0.90; 95% Confidence Interval: 0.80, 1.02; p=0.10).

Although there was no statistically significant difference between pioglitazone and placebo for the three-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with pioglitazone. The number of first occurrences and total individual events contributing to the primary composite endpoint is shown in *Table 6*.

Table 6. PROactive: Number of First and Total Events for Each Component Within the Cardiovascular Composite Endpoint

	Placebo N=2633		**Pioglitazone** N=2605	
Cardiovascular Events	First Events n (%)	Total Events n	First Events n (%)	Total Events n
Any Event	572 (21.7)	900	514 (19.7)	803
All-Cause Mortality	122 (4.6)	186	110 (4.2)	177
Nonfatal Myocardial Infarction (MI)	118 (4.5)	157	105 (4)	131
Stroke	96 (3.6)	119	76 (2.9)	92
Acute Coronary Syndrome	63 (2.4)	78	42 (1.6)	65
Cardiac Intervention (CABG/PCI)	101 (3.8)	240	101 (3.9)	195
Major Leg Amputation	15 (0.6)	28	9 (0.3)	28
Leg Revascularization	57 (2.2)	92	71 (2.7)	115

CABG=coronary artery bypass grafting; PCI=percutaneous intervention

Weight Gain

Dose-related weight gain occurs when pioglitazone is used alone or in combination with other antidiabetic medications. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Edema

Edema induced from taking pioglitazone is reversible when pioglitazone is discontinued. The edema usually does not require hospitalization unless there is coexisting congestive heart failure.

Hepatic Effects

There has been no evidence of pioglitazone-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date. One randomized, double-blind, three-year trial comparing pioglitazone to glyburide as add-on to metformin and insulin therapy was specifically designed to evaluate the incidence of serum ALT elevation to greater than three times the upper limit of the reference range, measured every eight weeks for the first 48 weeks of the trial then every 12 weeks thereafter. A total of 3/1051 (0.3%) patients treated with pioglitazone and 9/1046 (0.9%) patients treated with glyburide developed ALT values greater than three times the upper limit of the reference range. None of the patients treated with pioglitazone in the pioglitazone controlled clinical trial database to date have had

a serum ALT greater than three times the upper limit of the reference range and a corresponding total bilirubin greater than two times the upper limit of the reference range, a combination predictive of the potential for severe drug-induced liver injury.

Hypoglycemia

In the pioglitazone clinical trials, adverse reactions of hypoglycemia were reported based on clinical judgment of the investigators and did not require confirmation with finger stick glucose testing. In the 16 week add-on to sulfonylurea trial, the incidence of reported hypoglycemia was 3.7% with pioglitazone 30 mg and 0.5% with placebo. In the 16 week add-on to insulin trial, the incidence of reported hypoglycemia was 7.9% with pioglitazone 15 mg, 15.4% with pioglitazone 30 mg and 4.8% with placebo. The incidence of reported hypoglycemia was higher with pioglitazone 45 mg compared to pioglitazone 30 mg in both the 24 week add-on to sulfonylurea trial (15.7% versus 13.4%) and in the 24 week add-on to insulin trial (47.8% versus 43.5%). Three patients in these four trials were hospitalized due to hypoglycemia. All three patients were receiving pioglitazone 30 mg (0.9%) in the 24 week add-on to insulin trial. An additional 14 patients reported severe hypoglycemia (defined as causing considerable interference with patient's usual activities) that did not require hospitalization. These patients were receiving pioglitazone 45 mg in combination with sulfonylurea (N=2) or pioglitazone 30 mg or 45 mg in combination with insulin (N=12).

Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study *[see Nonclinical Toxicology (13.1)].* During the three year PROactive clinical trial, 14 patients out of 2605 (0.54%) randomized to pioglitazone and 5 out of 2633 (0.19%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 6 (0.23%) cases on pioglitazone and two (0.08%) cases on placebo. After completion of the trial, a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROactive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR =1.00; 95% CI: 0.59-1.72) *[see Warnings and Precautions (5.7)]*.

6.2 Laboratory Abnormalities

Pioglitazone

Hematologic Effects

Pioglitazone may cause decreases in hemoglobin and hematocrit. In placebo-controlled monotherapy trials, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone compared with a mean change in hemoglobin of -1% to +1% in placebo-treated patients. These changes primarily occurred within the first four to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and are not likely to be associated with any clinically significant hematologic effects.

Creatine Phosphokinase

During protocol-specified measurement of serum creatine phosphokinase (CPK) in pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in nine (0.2%) patients treated with pioglitazone (values of 2150 to 11400 IU/L) and in no comparator-treated patients. Six of these nine patients continued to receive pioglitazone, two patients were noted to have the CPK elevation on the last day of dosing and one patient discontinued pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

6.3 Postmarketing Experience

Alogliptin

The following adverse reactions have been identified during the postmarketing use of alogliptin. 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.

Acute pancreatitis, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria and severe cutaneous adverse reactions, including Stevens-Johnson syndrome, hepatic enzyme elevations, fulminant hepatic failure, severe and disabling arthralgia and bullous pemphigoid , diarrhea, constipation, nausea and ileus *[see Warnings and Precautions (5.2, 5.3, 5.4, 5.10, 5.11)]*.

Pioglitazone

The following adverse reactions have been identified during the postmarketing use of pioglitazone. 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.

New onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions (5.9)]*.

Fatal and nonfatal hepatic failure *[see Warnings and Precautions (5.4)].*

Postmarketing reports of congestive heart failure have been reported in patients treated with pioglitazone, both with and without previously known heart disease and both with and without concomitant insulin administration.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure *[see Boxed Warning and Warnings and Precautions (5.1)].*

7 DRUG INTERACTIONS

Alogliptin

Alogliptin is primarily renally excreted. Cytochrome (CYP) P450-related metabolism is negligible. No significant drug-drug interactions were observed with the CYP-substrates or inhibitors tested or with renally excreted drugs *[see Clinical Pharmacology (12.3)]*.

7.1 Strong CYP2C8 Inhibitors

Pioglitazone

An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the concentration-time curve [AUC]) and half-life of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

7.2 CYP2C8 Inducers

Pioglitazone

An inducer of CYP2C8 (e.g., rifampin) may significantly decrease the exposure (AUC) of pioglitazone. Therefore, if an inducer of CYP2C8 is started or stopped during treatment with OSENI, changes in diabetes treatment may be needed based on clinical response without exceeding the maximum recommended daily dose of 45 mg for pioglitazone *[see Clinical Pharmacology (12.3)]*.

7.3 Topiramate

Pioglitazone

A decrease in the exposure of pioglitazone and its active metabolites were noted with concomitant administration of pioglitazone and topiramate *[see Clinical Pharmacology (12.3)]*. The clinical relevance of this decrease is unknown; however, when OSENI and topiramate are used concomitantly, monitor patients for adequate glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with OSENI in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations].*

In animal reproduction studies, no adverse developmental effects were observed when pioglitazone was administered to pregnant rats and rabbits during organogenesis at exposures up to 5 and 35 times the 45 mg clinical dose, respectively, based on body surface area. No adverse developmental effects were observed when alogliptin was administered to pregnant rats and rabbits during organogenesis at exposures 180 and 149 times the 25 mg clinical dose, respectively, based on plasma drug exposure (AUC) *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. 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.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

Alogliptin and Pioglitazone

Co-administration of 100 mg/kg alogliptin and 40 mg/kg pioglitazone (39 and 10 times the 25 mg and 45 mg clinical doses, respectively, based on body surface area) to pregnant rats during organogenesis slightly augmented pioglitazone-related fetal effects of delayed development and reduced fetal weights but did not result in embryofetal mortality or teratogenicity.

Alogliptin

Alogliptin administered to pregnant rabbits and rats during the period of organogenesis did not cause adverse developmental effects at doses of up to 200 mg/kg and 500 mg/kg, or 149 times and 180 times, the 25 mg clinical dose, respectively, based on plasma drug exposure (AUC). Placental transfer of alogliptin into the fetus was observed following oral dosing to pregnant rats.

No adverse developmental outcomes were observed in offspring when alogliptin was administered to pregnant rats during gestation and lactation at doses up to 250 mg/kg (~95 times the 25 mg clinical dose, based on AUC).

Pioglitazone
Pioglitazone administered to pregnant rats during organogenesis did not cause adverse developmental effects at a dose of 20 mg/kg (~5-times the 45 mg clinical dose), but delayed parturition and reduced embryofetal viability at 40 and 80 mg/kg, or ≥9-times the 45 mg clinical dose, by body surface area. In pregnant rabbits administered pioglitazone during organogenesis, no adverse developmental effects were observed at 80 mg/kg (~35-times the 45 mg clinical dose), but reduced embryofetal viability at 160 mg/kg, or ~69-times the 45 mg clinical dose, by body surface area. When pregnant rats received pioglitazone during late gestation and lactation, delayed postnatal development, attributed to decreased body weight, occurred in offspring at maternal doses of 10 mg/kg and above or ≥2 times the 45 mg clinical dose, by body surface area.

8.2 Lactation
Risk Summary
There is no information regarding the presence of pioglitazone or alogliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Pioglitazone and alogliptin are present in rat milk; however, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OSENI and any potential adverse effects on the breastfed infant from OSENI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some anovulatory women.

8.4 Pediatric Use
Safety and effectiveness of OSENI in pediatric patients have not been established.

OSENI is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures and urinary bladder tumors *[see Warnings and Precautions (5.1, 5.5, 5.6, 5.7)]*.

8.5 Geriatric Use
Alogliptin and Pioglitazone
Of the total number of patients (N=1533) in clinical safety and efficacy studies treated with alogliptin and pioglitazone, 248 (16.2%) patients were 65 years and older and 15 (1%) patients were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this and other reported clinical experiences have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be excluded.

Alogliptin
Of the total number of patients (N=9052) in clinical safety and efficacy studies treated with alogliptin, 2257 (24.9%) patients were ≥65 years old and 386 (4.3%) patients were ≥75 years old. No overall differences in safety or effectiveness were observed between patients ≥65 years old and younger patients.

Pioglitazone
A total of 92 patients (15.2%) treated with pioglitazone in the three pooled, 16 to 26 week, double-blind, placebo-controlled, monotherapy trials were ≥65 years old and two patients (0.3%) were ≥75 years old. In the two pooled 16 to 24 week add-on to sulfonylurea trials, 201 patients (18.7%) treated with pioglitazone were ≥65 years old and 19 (1.8%) were ≥75 years old. In the two pooled 16 to 24 week add-on to metformin trials, 155 patients (15.5%) treated with pioglitazone were ≥65 years old

and 19 (1.9%) were ≥75 years old. In the two pooled 16 to 24 week add-on to insulin trials, 272 patients (25.4%) treated with pioglitazone were ≥65 years old and 22 (2.1%) were ≥75 years old.

In PROactive, 1068 patients (41%) treated with pioglitazone were ≥65 years old and 42 (1.6%) were ≥75 years old.

In pharmacokinetic studies with pioglitazone, no significant differences were observed in pharmacokinetic parameters between elderly and younger patients. These clinical experiences have not identified differences in effectiveness and safety between the elderly (≥65 years) and younger patients although small sample sizes for patients ≥75 years old limit conclusions *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Alogliptin

A total of 602 patients with moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73 m^2) and four patients with severe renal impairment/end-stage renal disease (eGFR <30 mL/min/1.73 m^2 or <15 mL/min/1.73 m^2, respectively) at baseline were treated with alogliptin in clinical trials in patients with type 2 diabetes. Reductions in HbA1c were generally similar in this subgroup of patients. The overall incidence of adverse reactions was generally balanced between alogliptin and placebo treatments in this subgroup of patients.

In the EXAMINE trial of high CV risk type 2 diabetes patients, 694 patients had moderate renal impairment and 78 patients had severe renal impairment or end-stage renal disease at baseline. The overall incidences of adverse reactions, serious adverse reactions and adverse reactions leading to study drug discontinuation were generally similar between the treatment groups.

8.7 Hepatic Impairment

Alogliptin

No dose adjustments are required in patients with mild to moderate hepatic impairment (Child-Pugh Grade A and B) based on insignificant change in systemic exposures (e.g., AUC) compared to subjects with normal hepatic function in a pharmacokinetic study. Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh Grade C). Use caution when administering alogliptin to patients with liver disease *[see Warnings and Precautions (5.4)].*

Pioglitazone

No dose adjustments are required in patients with hepatic impairment (Child-Pugh Grade B and C) based on insignificant change in systemic exposures (e.g., AUC) compared to subjects with normal hepatic function in a pharmacokinetic study. However, use with caution in patients with liver disease *[see Warnings and Precautions (5.4)].*

10 OVERDOSAGE

Alogliptin

The highest doses of alogliptin administered in clinical trials were single doses of 800 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type 2 diabetes (equivalent to 32 times and 16 times the maximum recommended clinical dose of 25 mg, respectively). No serious adverse reactions were observed at these doses.

In the event of an overdose, it is reasonable to institute the necessary clinical monitoring and supportive therapy as dictated by the patient's clinical status. Per clinical judgment, it may be reasonable to initiate removal of unabsorbed material from the gastrointestinal tract.

Alogliptin is minimally dialyzable; over a three-hour hemodialysis session, approximately 7% of the drug was removed. Therefore, hemodialysis is unlikely to be beneficial in an overdose situation. It is not known if alogliptin is dialyzable by peritoneal dialysis.

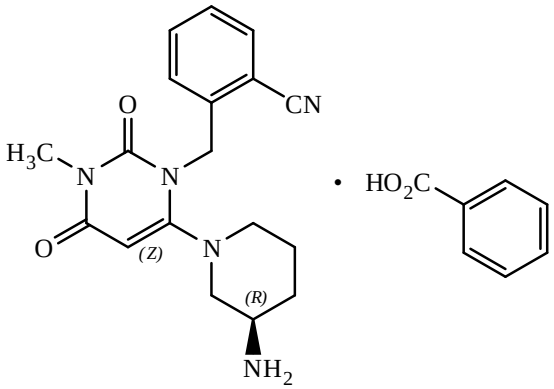
Pioglitazone
During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

11 DESCRIPTION

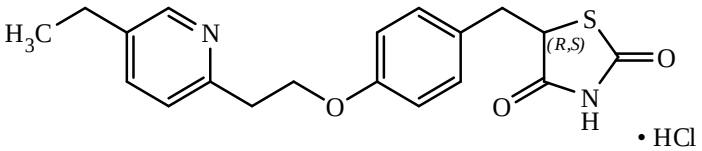
OSENI tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: alogliptin and pioglitazone.

Alogliptin
Alogliptin is a selective, orally bioavailable inhibitor of the enzymatic activity of dipeptidyl peptidase-4 (DPP-4). Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)benzonitrile monobenzoate. It has a molecular formula of $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$ and a molecular weight of 461.51 daltons. The structural formula is:



Alogliptin benzoate is a white to off-white crystalline powder containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol and very slightly soluble in octanol and isopropyl acetate.

Pioglitazone
Pioglitazone is an oral antihyperglycemic agent that acts primarily by decreasing insulin resistance. Chemically, pioglitazone is prepared as hydrochloride salt, which is identified as (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride. It has a molecular formula of $C_{19}H_{20}N_2O_3S \cdot HCl$ and a molecular weight of 392.90 daltons. The structural formula is:



Pioglitazone hydrochloride is an odorless white crystalline powder that contains one asymmetric carbon in the thiazolidinedione moiety. The synthetic compound is a racemate and the two enantiomers of pioglitazone interconvert *in vivo*. It is soluble in *N,N* dimethylformamide, slightly

soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water and insoluble in ether.

OSENI is available as a fixed-dose combination tablet for oral administration containing 34 mg alogliptin benzoate equivalent to 25 mg alogliptin and any of the following strengths of pioglitazone hydrochloride:

- 16.53 mg pioglitazone hydrochloride equivalent to 15 mg pioglitazone (25 mg/15 mg)
- 33.06 mg pioglitazone hydrochloride equivalent to 30 mg pioglitazone (25 mg/30 mg)
- 49.59 mg pioglitazone hydrochloride equivalent to 45 mg pioglitazone (25 mg/45 mg)

OSENI is also available as a fixed-dose combination tablet for oral administration containing 17 mg alogliptin benzoate equivalent to 12.5 mg alogliptin and any of the following strengths of pioglitazone hydrochloride:

- 16.53 mg pioglitazone hydrochloride equivalent to 15 mg pioglitazone (12.5 mg/15 mg)
- 33.06 mg pioglitazone hydrochloride equivalent to 30 mg pioglitazone (12.5 mg/30 mg)
- 49.59 mg pioglitazone hydrochloride equivalent to 45 mg pioglitazone (12.5 mg/45 mg)

OSENI tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate and lactose monohydrate; the tablets are film-coated with hypromellose, polyethylene glycol, titanium dioxide, talc and ferric oxide (yellow and/or red) and are marked with printing ink (Red A1 or Gray F1).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

OSENI combines two antihyperglycemic agents with complementary and distinct mechanisms of action to improve glycemic control in patients with type 2 diabetes: alogliptin, a selective inhibitor of DPP-4, and pioglitazone, a member of the TZD class.

Alogliptin

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Alogliptin is a DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus. Alogliptin selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Pioglitazone

Pharmacologic studies indicate that pioglitazone improves insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin- responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Because pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

12.2 Pharmacodynamics

Alogliptin and Pioglitazone

In a 26 week, randomized, active-controlled study, patients with type 2 diabetes received alogliptin 25 mg coadministered with pioglitazone 30 mg, alogliptin 12.5 mg coadministered with pioglitazone 30 mg, alogliptin 25 mg alone or pioglitazone 30 mg alone. Patients who were randomized to alogliptin 25 mg with pioglitazone 30 mg achieved a 26.2% decrease in triglyceride levels from a mean baseline of 214.2 mg/dL compared to an 11.5% decrease for alogliptin alone and a 21.8% decrease for pioglitazone alone. In addition, a 14.4% increase in HDL cholesterol levels from a mean baseline of 43.2 mg/dL was also observed for alogliptin 25 mg with pioglitazone 30 mg compared to a 1.9% increase for alogliptin alone and a 13.2% increase for pioglitazone alone. The changes in measures of LDL cholesterol and total cholesterol were similar between alogliptin 25 mg with pioglitazone 30 mg versus alogliptin alone and pioglitazone alone. A similar pattern of lipid effects was observed in a 26 week, placebo-controlled factorial study.

Alogliptin

Single-dose administration of alogliptin to healthy subjects resulted in a peak inhibition of DPP-4 within two to three hours after dosing. The peak inhibition of DPP-4 exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses greater than or equal to 25 mg. Peak and total exposure over 24 hours to active GLP-1 were three- to four-fold greater with alogliptin (at doses of 25 to 200 mg) than placebo. In a 16 week, double-blind, placebo-controlled study alogliptin 25 mg demonstrated decreases in postprandial glucagon while increasing postprandial active GLP-1 levels compared to placebo over an eight-hour period following a standardized meal. It is unclear how these findings relate to changes in overall glycemic control in patients with type 2 diabetes mellitus. In this study, alogliptin 25 mg demonstrated decreases in two-hour postprandial glucose compared to placebo (-30 mg/dL versus 17 mg/dL respectively).

Multiple-dose administration of alogliptin to patients with type 2 diabetes also resulted in a peak inhibition of DPP-4 within one to two hours and exceeded 93% across all doses (25 mg, 100 mg and 400 mg) after a single dose and after 14 days of once-daily dosing. At these doses of alogliptin, inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing.

Pioglitazone

Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations and lower A1C values. In controlled clinical trials, pioglitazone had an additive effect on glycemic control when used in combination with a sulfonylurea, metformin or insulin *[see Clinical Studies (14)]*. Patients with lipid abnormalities were included in clinical trials with pioglitazone. Overall, patients treated with pioglitazone had mean decreases in serum triglycerides, mean increases in HDL cholesterol and no consistent mean changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular benefit with pioglitazone *[see Warnings and Precautions (5.12) and Adverse Reactions (6.1)]*.

In a 26 week, placebo-controlled, dose-ranging monotherapy study, mean serum triglycerides decreased in the pioglitazone 15 mg, 30 mg and 45 mg dose groups compared to a mean increase in the placebo group. Mean HDL cholesterol increased to a greater extent in patients treated with pioglitazone than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with pioglitazone compared to placebo *(Table 7)*.

Table 7. Lipids in a 26 Week, Placebo-Controlled, Monotherapy, Dose-Ranging Study

	Placebo	**Pioglitazone 15 mg Once Daily**	**Pioglitazone 30 mg Once Daily**	**Pioglitazone 45 mg Once Daily**
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	263	284	261	260
Percent change from baseline (adjusted mean*)	4.8%	-9%†	-9.6%†	-9.3%†
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	42	40	41	41
Percent change from baseline (adjusted mean*)	8.1%	14.1%†	12.2%	19.1%†
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	139	132	136	127
Percent change from baseline (adjusted mean*)	4.8%	7.2%	5.2%	6%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	225	220	223	214
Percent change from baseline (adjusted mean*)	4.4%	4.6%	3.3%	6.4%

*Adjusted for baseline, pooled center and pooled center by treatment interaction
†$p<0.05$ versus placebo

In the two other monotherapy studies (16 weeks and 24 weeks) and in combination therapy studies with sulfonylurea (16 weeks and 24 weeks), metformin (16 weeks and 24 weeks) or insulin (16 weeks and 24 weeks), the lipid results were generally consistent with the data above.

12.3 Pharmacokinetics

Absorption and Bioavailability

Alogliptin and Pioglitazone

In bioequivalence studies of OSENI, the area under the plasma concentration curve (AUC) and maximum concentration (C_{max}) of both the alogliptin and the pioglitazone component following a single dose of the combination tablet (12.5 mg/15 mg or 25 mg/45 mg) were bioequivalent to alogliptin (12.5 mg or 25 mg) concomitantly administered with pioglitazone (15 mg or 45 mg respectively) tablets under fasted conditions in healthy subjects.

Administration of OSENI 25 mg/45 mg with food resulted in no significant change in overall exposure of alogliptin or pioglitazone. OSENI may therefore be administered with or without food.

Alogliptin
The absolute bioavailability of alogliptin is approximately 100%. Administration of alogliptin with a high-fat meal results in no significant change in total and peak exposure to alogliptin. Alogliptin may therefore be administered with or without food.

Pioglitazone
Following oral administration of pioglitazone hydrochloride, peak concentrations of pioglitazone were observed within two hours. Food slightly delays the time to peak serum concentration (T_{max}) to three to four hours but does not alter the extent of absorption (AUC).

Distribution
Alogliptin
Following a single, 12.5 mg intravenous infusion of alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L, indicating that the drug is well distributed into tissues.

Alogliptin is 20% bound to plasma proteins.

Pioglitazone
The mean apparent V_d/F of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

Metabolism
Alogliptin
Alogliptin does not undergo extensive metabolism and 60% to 71% of the dose is excreted as unchanged drug in the urine.

Two minor metabolites were detected following administration of an oral dose of [^{14}C] alogliptin, *N*-demethylated, M-I (less than 1% of the parent compound), and *N*-acetylated alogliptin, M-II (less than 6% of the parent compound). M-I is an active metabolite and is an inhibitor of DPP-4 similar to the parent molecule; M-II does not display any inhibitory activity toward DPP-4 or other DPP-related enzymes. *In vitro* data indicate that CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

Alogliptin exists predominantly as the (*R*)-enantiomer (more than 99%) and undergoes little or no chiral conversion *in vivo* to the (*S*)-enantiomer. The (*S*)-enantiomer is not detectable at the 25 mg dose.

Pioglitazone
Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans. Following once-daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within seven days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. At steady-state, in both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations (pioglitazone plus active metabolites) and 20% to 25% of the total AUC.

Maximum serum concentration (C_{max}), AUC and trough serum concentrations (C_{min}) for pioglitazone and M-III and M-IV, increased proportionally with administered doses of 15 mg and 30 mg per day.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms, including the mainly extrahepatic CYP1A1. *In vivo* studies of pioglitazone in combination with gemfibrozil, a strong CYP2C8 inhibitor, showed that pioglitazone is a CYP2C8 substrate *[see Dosage and Administration (2.3) and Drug Interactions (7)]*. Urinary 6β-hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination

Alogliptin

The primary route of elimination of [^{14}C] alogliptin derived radioactivity occurs via renal excretion (76%) with 13% recovered in the feces, achieving a total recovery of 89% of the administered radioactive dose. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr.

Pioglitazone

Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Special Populations

Renal Impairment

Alogliptin

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of alogliptin 50 mg in patients with chronic renal impairment compared with healthy subjects.

In patients with mild renal impairment (creatinine clearance [CrCl] ≥60 to <90 mL/min), an approximate 1.2-fold increase in plasma AUC of alogliptin was observed. Because increases of this magnitude are not considered clinically relevant, dose adjustment for patients with mild renal impairment is not recommended.

In patients with moderate renal impairment (CrCl ≥30 to <60 mL/min), an approximate two-fold increase in plasma AUC of alogliptin was observed. To maintain similar systemic exposures of OSENI to those with normal renal function, the recommended dose of OSENI is 12.5 mg/15 mg, 12.5 mg/30 mg or 12.5 mg/45 mg once daily in patients with moderate renal impairment.

In patients with severe renal impairment (CrCl ≥15 to <30 mL/min) and end-stage renal disease (ESRD) (CrCl <15 mL/min or requiring dialysis), an approximate three- and four-fold increase in plasma AUC of alogliptin were observed, respectively. Dialysis removed approximately 7% of the drug during a three-hour dialysis session. OSENI is not recommended for patients with severe renal impairment or ESRD. Coadministration of pioglitazone and alogliptin 6.25 mg once daily based on individual requirements may be considered in these patients.

Pioglitazone

The serum elimination half-life of pioglitazone, M-III and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 50 mL/min) to severe (creatinine clearance <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore no dose adjustment in patients with renal impairment is required.

Hepatic Impairment

Alogliptin

Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment (Child-Pugh Grade B) compared to healthy subjects. The magnitude of these reductions is not considered to be clinically meaningful. Patients with severe hepatic impairment (Child-Pugh Grade C) have not been studied. Use caution when administering OSENI to patients with liver disease *[see Use in Specific Populations (8.7) and Warnings and Precautions (5.4)]*.

Pioglitazone

Compared with healthy controls, subjects with impaired hepatic function (Child-Pugh Grade B and C) have an approximate 45% reduction in pioglitazone and total pioglitazone (pioglitazone, M-III and M-IV) mean peak concentrations but no change in the mean AUC values. Therefore, no dose adjustment in patients with hepatic impairment is required.

There are postmarketing reports of liver failure with pioglitazone and clinical trials have generally excluded patients with serum ALT >2.5 times the upper limit of the reference range. Use caution in patients with liver disease *[see Warnings and Precautions (5.4)].*

Gender

Alogliptin

No dose adjustment of alogliptin is necessary based on gender. Gender did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Pioglitazone

The mean C_{max} and AUC values of pioglitazone were increased 20% to 60% in women compared to men. In controlled clinical trials, A1C decreases from baseline were generally greater for females than for males (average mean difference in A1C 0.5%). Because therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Geriatric

Alogliptin

No dose adjustment of alogliptin is necessary based on age. Age did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Pioglitazone

In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are approximately 21% higher than those achieved in younger subjects. The mean terminal half-life values of pioglitazone were also longer in elderly subjects (about 10 hours) as compared to younger subjects (about seven hours). These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics

Alogliptin

Studies characterizing the pharmacokinetics of alogliptin in pediatric patients have not been performed.

Pioglitazone

Safety and efficacy of pioglitazone in pediatric patients have not been established. Pioglitazone is not recommended for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

Race and Ethnicity

Alogliptin

No dose adjustment of alogliptin is necessary based on race. Race (White, Black and Asian) did not have any clinically meaningful effect on the pharmacokinetics of alogliptin.

Pioglitazone

Pharmacokinetic data among various ethnic groups are not available.

Drug Interactions

Coadministration of alogliptin 25 mg once daily with a CYP2C8 substrate, pioglitazone 45 mg once daily for 12 days had no clinically meaningful effects on the pharmacokinetics of pioglitazone and its active metabolites.

Specific pharmacokinetic drug interaction studies with OSENI have not been performed, although such studies have been conducted with the individual components of OSENI (alogliptin and pioglitazone).

Alogliptin

In Vitro Assessment of Drug Interactions

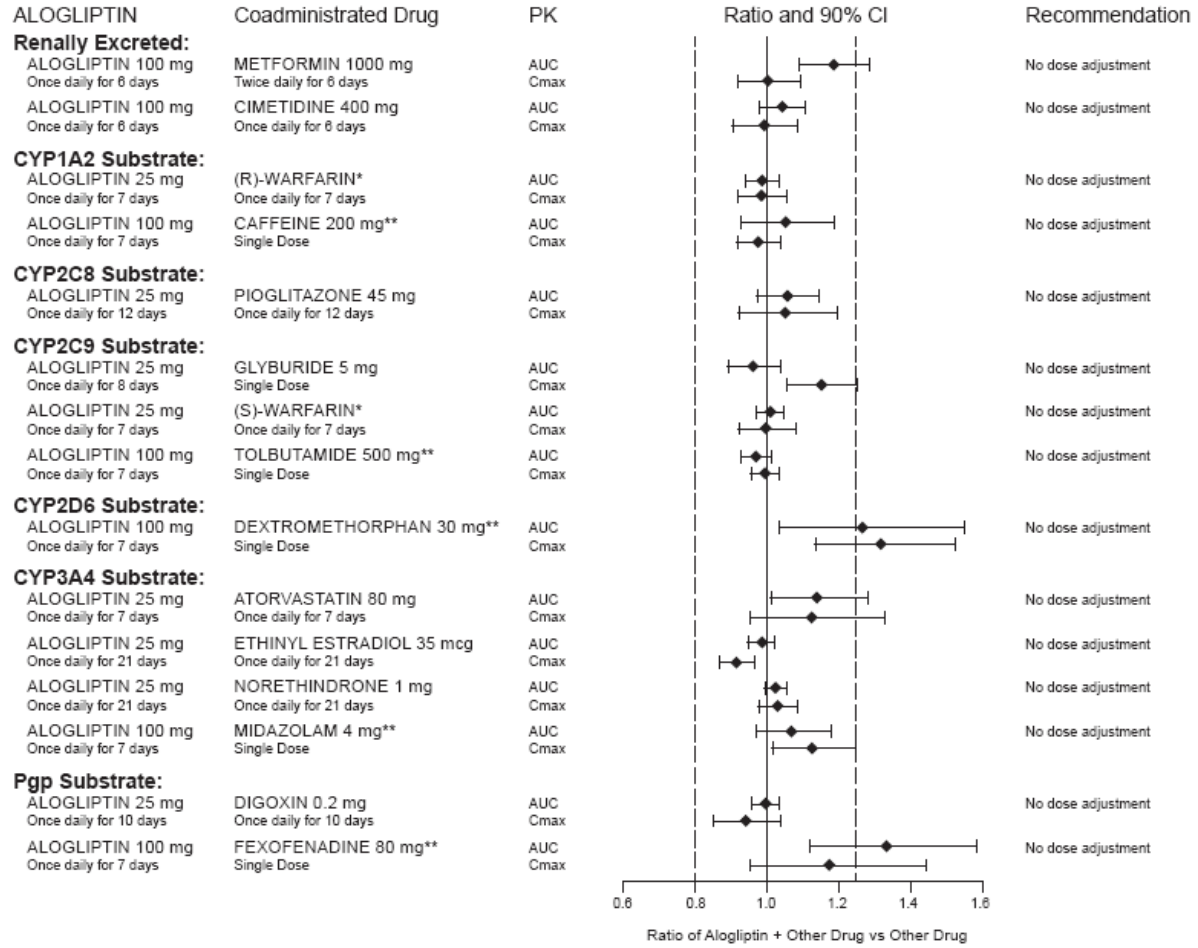
In vitro studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions

Effects of Alogliptin on the Pharmacokinetics of Other Drugs

In clinical studies, alogliptin did not meaningfully increase the systemic exposure to the following drugs that are metabolized by CYP isozymes or excreted unchanged in urine *(Figure 1)*. No dose adjustment of alogliptin is recommended based on results of the described pharmacokinetic studies.

Figure 1. Effect of Alogliptin on the Pharmacokinetic Exposure to Other Drugs

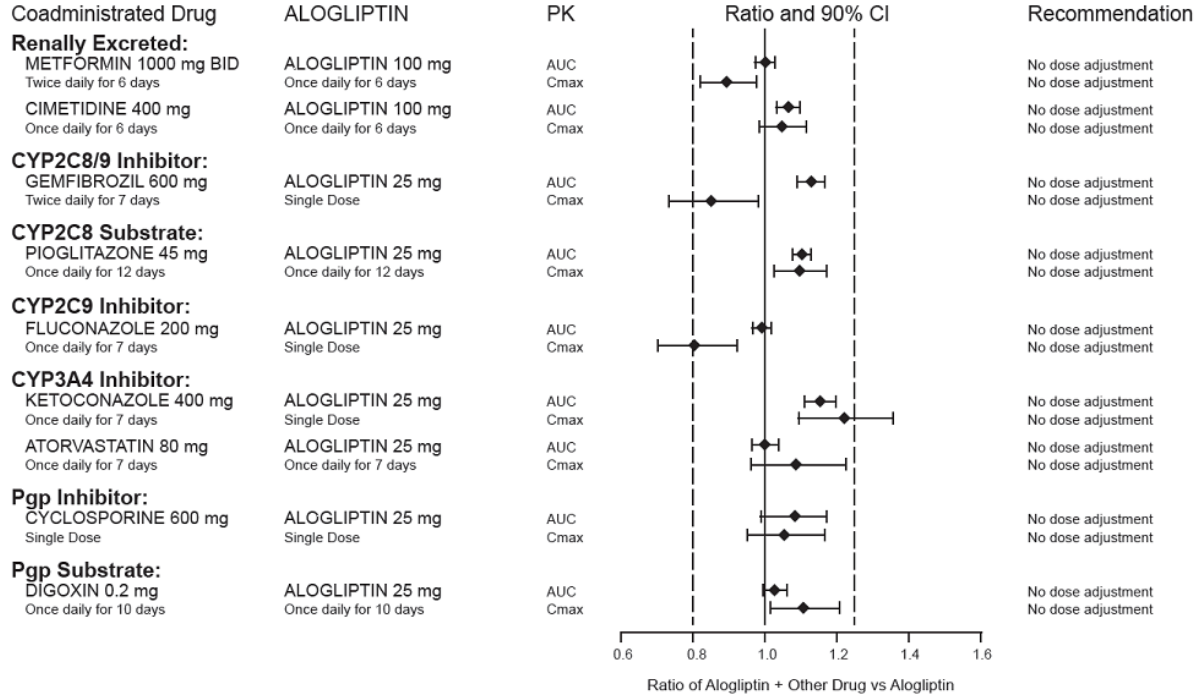


*Warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).
**Caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam (3A4 substrate) and fexofenadine (P-gp substrate) were administered as a cocktail.

Effects of Other Drugs on the Pharmacokinetics of Alogliptin

There are no clinically meaningful changes in the pharmacokinetics of alogliptin when alogliptin is administered concomitantly with the drugs described below *(Figure 2).*

Figure 2. Effect of Other Drugs on the Pharmacokinetic Exposure of Alogliptin



Pioglitazone

Table 8. Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs					
	Coadministered Drug				
Pioglitazone Dosage Regimen (mg)*	**Name and Dose Regimens**	**Change in AUC†**		**Change in C_{max}†**	
45 mg (N=12)	**Warfarin‡**				
	Daily loading then maintenance doses based PT and INR values Quick's Value=35 ± 5%	R-Warfarin	↓3%	R-Warfarin	↓2%
		S-Warfarin	↓1%	S-Warfarin	↑1%
45 mg (N=12)	**Digoxin**				
	0.200 mg twice daily (loading dose) then 0.250 mg daily (maintenance dose, 7 days)	↑15%		↑17%	
45 mg daily for 21 days (N=35)	**Oral Contraceptive**				
	[Ethinyl Estradiol (EE) 0.035 mg plus Norethindrone (NE) 1 mg] for 21 days	EE	↓11%	EE	↓13%
		NE	↑3%	NE	↓7%
45 mg (N=23)	**Fexofenadine**				
	60 mg twice daily for 7 days	↑30%		↑37%	
45 mg (N=14)	**Glipizide**				
	5 mg daily for 7 days	↓3%		↓8%	
45 mg daily for 8 days (N=16)	**Metformin**				
	1000 mg single dose on 8 days	↓3%		↓5%	
45 mg (N=21)	**Midazolam**				
	7.5 mg single dose on day 15	↓26%		↓26%	
45 mg (N=24)	**Ranitidine**				
	150 mg twice daily for 7 days	↑1%		↓1%	
45 mg daily for 4 days (N=24)	**Nifedipine ER**				
	30 mg daily for 4 days	↓13%		↓17%	
45 mg (N=25)	**Atorvastatin Ca**				
	80 mg daily for 7 days	↓14%		↓23%	
45 mg (N=22)	**Theophylline**				
	400 mg twice daily for 7 days	↑2%		↑5%	

*Daily for seven days unless otherwise noted
†% change (with/without coadministered drug and no change=0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively
‡Pioglitazone had no clinically significant effect on prothrombin time

Table 9. Effect of Coadministered Drugs on Pioglitazone Systemic Exposure			
Coadministered Drug and Dosage Regimen	**Pioglitazone**		
	Dose Regimen (mg)*	**Change in AUC†**	**Change in C_{max}†**
Gemfibrozil 600 mg twice daily for 2 days (N=12)	30 mg single dose	↑3.4-fold‡	↑6%
Ketoconazole 200 mg twice daily for 7 days (N=28)	45 mg	↑34%	↑14%
Rifampin 600 mg daily for 5 days (N=10)	30 mg single dose	↓54%	↓5%
Fexofenadine 60 mg twice daily for 7 days (N=23)	45 mg	↑1%	0%
Ranitidine 150 mg twice daily for 4 days (N=23)	45 mg	↓13%	↓16%
Nifedipine ER 30 mg daily for 7 days (N=23)	45 mg	↑5%	↑4%
Atorvastatin Ca 80 mg daily for 7 days (N=24)	45 mg	↓24%	↓31%
Theophylline 400 mg twice daily for 7 days (N=22)	45 mg	↓4%	↓2%
Topiramate 96 mg twice daily for 7 days§ (N=26)	30 mg §	↓15%¶	0%

*Daily for seven days unless otherwise noted
†Mean ratio (with/without coadministered drug and no change=one-fold) % change (with/without coadministered drug and no change=0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively
‡The half-life of pioglitazone increased from 6.5 hours to 15.1 hours in the presence of gemfibrozil *[see Dosage and Administration (2.3) and Drug Interactions (7)]*
§Indicates duration of concomitant administration with highest twice-daily dose of topiramate from Day 14 onwards over the 22 days of study
¶Additional decrease in active metabolites; 60% for M-III and 16% for M-IV

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Alogliptin and Pioglitazone
No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with OSENI. The following data are based on findings in studies performed with alogliptin or pioglitazone individually.

Alogliptin
Rats were administered oral doses of 75, 400 and 800 mg/kg alogliptin for two years. No drug-related tumors were observed up to 75 mg/kg or approximately 32 times the maximum recommended clinical dose of 25 mg, based on area under the plasma concentration curve (AUC) exposure. At higher doses (approximately 308 times the maximum recommended clinical dose of 25 mg), a combination of thyroid C-cell adenomas and carcinomas increased in male but not female rats. No drug-related tumors were observed in mice after administration of 50, 150 or 300 mg/kg alogliptin for two years, or up to approximately 51 times the maximum recommended clinical dose of 25 mg, based on AUC exposure.

Alogliptin was not mutagenic or clastogenic, with and without metabolic activation, in the Ames test with *S. typhimurium* and *E. coli* or the cytogenetic assay in mouse lymphoma cells. Alogliptin was negative in the *in vivo* mouse micronucleus study.

In a fertility study in rats, alogliptin had no adverse effects on early embryonic development, mating or fertility at doses up to 500 mg/kg, or approximately 172 times the clinical dose based on plasma drug exposure (AUC).

Pioglitazone
A two year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the MRHD of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg and above (approximately equal to the MRHD based on mg/m^2). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg (approximately 11 times the MRHD based on mg/m^2). No drug-induced tumors were observed in any organ.

Pioglitazone was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone daily prior to and throughout mating and gestation (approximately nine times the MRHD based on mg/m^2).

13.2 Animal Toxicology and/or Pharmacology

Pioglitazone
Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone (approximately 11, one, and two times the MRHD for mice, rats and dogs, respectively, based on mg/m^2). In a one year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg (approximately 35 times the MRHD based on mg/m^2). Heart enlargement was seen in a 13 week study in monkeys at oral doses of

8.9 mg/kg and above (approximately four times the MRHD based on mg/m^2), but not in a 52 week study at oral doses up to 32 mg/kg (approximately 13 times the MRHD based on mg/m^2).

14 CLINICAL STUDIES

The coadministration of alogliptin and pioglitazone has been studied in patients with type 2 diabetes inadequately controlled on either diet and exercise alone or on metformin alone.

There have been no clinical efficacy studies conducted with OSENI; however, bioequivalence of OSENI with coadministered alogliptin and pioglitazone tablets was demonstrated, and efficacy of the combination of alogliptin and pioglitazone has been demonstrated in four Phase 3 efficacy studies.

In patients with type 2 diabetes, treatment with OSENI produced clinically meaningful and statistically significant improvements in A1C compared to either alogliptin or pioglitazone alone. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with OSENI appears to be related to the degree of A1C elevation at baseline.

Alogliptin and Pioglitazone Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise

In a 26 week, double-blind, active-controlled study, a total of 655 patients inadequately controlled on diet and exercise alone (mean baseline A1C=8.8%) were randomized to receive alogliptin 25 mg alone, pioglitazone 30 mg alone, alogliptin 12.5 mg with pioglitazone 30 mg or alogliptin 25 mg with pioglitazone 30 mg once daily. Coadministration of alogliptin 25 mg with pioglitazone 30 mg resulted in statistically significant improvements from baseline in A1C and FPG compared to either alogliptin 25 mg alone or to pioglitazone 30 mg alone *(Table 10)*. Coadministration of alogliptin 25 mg with pioglitazone 30 mg once daily resulted in statistically significant reductions in fasting plasma glucose (FPG) starting from Week 2 through Week 26 compared to either alogliptin 25 mg or pioglitazone 30 mg alone. A total of 3% of patients receiving alogliptin 25 mg coadministered with pioglitazone 30 mg, 11% of those receiving alogliptin 25 mg alone, and 6% of those receiving pioglitazone 30 mg alone required glycemic rescue.

Improvements in A1C were not affected by gender, age or baseline BMI.

The mean increase in body weight was similar between pioglitazone alone and alogliptin when coadministered with pioglitazone.

Table 10. Glycemic Parameters at Week 26 in a Coadministration Study of Alogliptin and Pioglitazone in Patients Inadequately Controlled on Diet and Exercise*			
	Alogliptin 25 mg	**Pioglitazone 30 mg**	**Alogliptin 25 mg + Pioglitazone 30 mg**
A1C (%)	N=160	N=153	N=158
Baseline (mean)	8.8	8.8	8.8
Change from Baseline (adjusted mean[†])	-1	-1.2	-1.7
Difference from alogliptin 25 mg (adjusted mean[†] with 95% confidence interval)			-0.8[‡] (-1, -0.5)
Difference from pioglitazone 30 mg (adjusted mean[†] with 95% confidence interval)			-0.6[‡] (-0.8, -0.3)
% of Patients (n/N) achieving A1C ≤ 7%	24% (40/164)	34% (55/163)	63% (103/164)[‡]
FPG (mg/dL)	N=162	N=157	N=162
Baseline (mean)	189	189	185
Change from Baseline (adjusted mean[†])	-26	-37	-50
Difference from alogliptin 25 mg (adjusted mean[†] with 95% confidence interval)			-25[‡] (-34, -15)
Difference from pioglitazone 30 mg (adjusted mean[†] with 95% confidence interval)			-13[‡] (-22, -4)

*Intent-to-treat population using last observation carried forward
[†]Least squares means adjusted for treatment, geographic region and baseline value
[‡]$p<0.01$ compared to alogliptin 25 mg or pioglitazone 30 mg

Alogliptin and Pioglitazone Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone

In the second 26 week, double-blind, placebo-controlled study, a total of 1554 patients already on metformin (mean baseline A1C=8.5%) were randomized to one of 12 double-blind treatment groups: placebo; 12.5 mg or 25 mg of alogliptin alone; 15 mg, 30 mg or 45 mg of pioglitazone alone; or 12.5 mg or 25 mg of alogliptin in combination with 15 mg, 30 mg or 45 mg of pioglitazone. Patients were maintained on a stable dose of metformin (median dose=1700 mg) during the treatment period. Coadministration of alogliptin and pioglitazone provided statistically significant improvements in A1C and FPG compared to placebo, to alogliptin alone, or to pioglitazone alone when added to background metformin therapy *(Table 11, Figure 3)*. A total of 4%, 5% or 2% of patients receiving alogliptin 25 mg with 15 mg, 30 mg or 45 mg pioglitazone, 33% of patients receiving placebo, 13% of patients receiving alogliptin 25 mg, and 10%, 15% or 9% of patients receiving pioglitazone 15 mg, 30 mg or 45 mg alone required glycemic rescue.

Improvements in A1C were not affected by gender, age or baseline BMI.

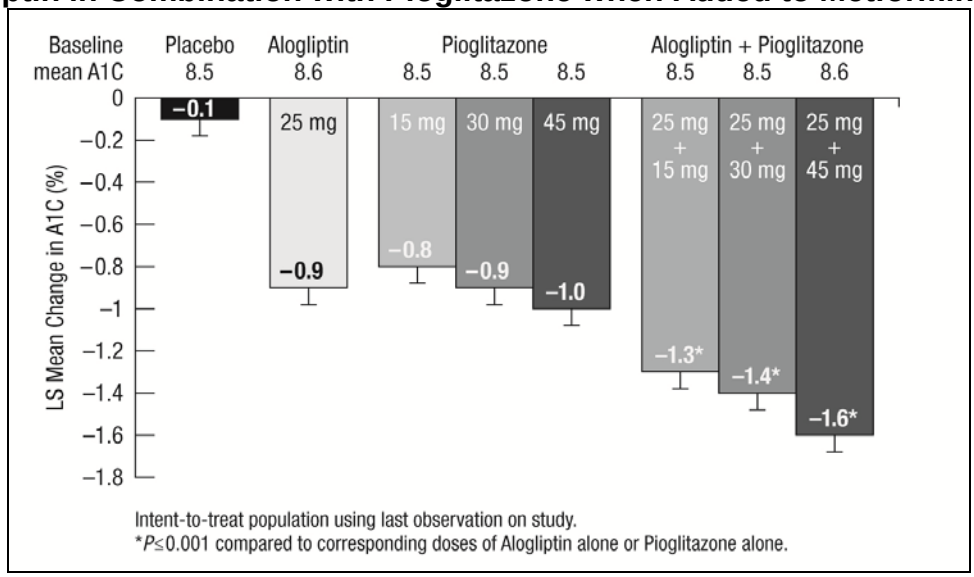
The mean increase in body weight was similar between pioglitazone alone and alogliptin when coadministered with pioglitazone.

Table 11. Glycemic Parameters at Week 26 for Alogliptin and Pioglitazone Alone and in Combination in Patients with Type 2 Diabetes*

	Placebo	**Alogliptin 25 mg**	**Pioglitazone 15 mg**	**Pioglitazone 30 mg**	**Pioglitazone 45 mg**	**Alogliptin 25 mg + Pioglitazone 15 mg**	**Alogliptin 25 mg + Pioglitazone 30 mg**	**Alogliptin 25 mg + Pioglitazone 45 mg**
A1C (%)	N=126	N=123	N=127	N=123	N=126	N=127	N=124	N=126
Baseline (mean)	8.5	8.6	8.5	8.5	8.5	8.5	8.5	8.6
Change from baseline (adjusted mean† with 95% confidence interval)	-0.1	-0.9	-0.8	-0.9	-1	-1.3‡	-1.4‡	-1.6‡
Difference from pioglitazone (adjusted mean† with 95% confidence interval)	-	-	-	-	-	-0.5‡ (-0.7, -0.3)	-0.5‡ (-0.7, -0.3)	-0.6‡ (-0.8, -0.4)
Difference from alogliptin (adjusted mean† with 95% confidence interval)	-	-	-	-	-	-0.4‡ (-0.6, -0.1)	-0.5‡ (-0.7, -0.3)	-0.7‡ (-0.9, -0.5)
Patients (%) achieving A1C ≤7%	6% (8/129)	27% (35/129)	26% (33/129)	30% (38/129)	36% (47/129)	55% (71/130)‡	53% (69/130)‡	60% (78/130)‡
FPG (mg/dL)	N=129	N=126	N=127	N=125	N=129	N=130	N=126	N=127
Baseline (mean)	177	184	177	175	181	179	179	178
Change from baseline (adjusted mean† with 95% confidence interval)	7	-19	-24	-29	-32	-38‡	-42‡	-53‡
Difference from pioglitazone (adjusted mean† with 95% confidence interval)	-	-	-	-	-	-14‡ (-24, -5)	-13‡ (-23, -3)	-20‡ (-30, -11)
Difference from alogliptin (adjusted mean† with 95% confidence interval)	-	-	-	-	-	-19‡ (-29, -10)	-23‡ (-33, -13)	-34‡ (-44, -24)

*Intent-to-treat population using last observation carried forward
†Least squares means adjusted for treatment, geographic region metformin dose and baseline value
‡p≤0.01 when compared to pioglitazone and alogliptin alone

Figure 3. Change from Baseline in A1C at Week 26 with Alogliptin and Pioglitazone Alone and Alogliptin in Combination with Pioglitazone when Added to Metformin



Alogliptin Add-On Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin in Combination with Pioglitazone

In a 52 week, active-comparator study, a total of 803 patients inadequately controlled (mean baseline A1C=8.2%) on a current regimen of pioglitazone 30 mg and metformin at least 1500 mg per day or at the maximum tolerated dose were randomized to either receive the addition of alogliptin 25 mg or the titration of pioglitazone 30 mg to 45 mg following a four week, single-blind, placebo run-in period. Patients were maintained on a stable dose of metformin (median dose=1700 mg). Patients who failed to meet prespecified hyperglycemic goals during the 52 week treatment period received glycemic rescue therapy.

In combination with pioglitazone and metformin, alogliptin 25 mg was shown to be statistically superior in lowering A1C and FPG compared with the titration of pioglitazone from 30 mg to 45 mg at Week 26 and Week 52 *(Table 12, results shown only for Week 52)*. A total of 11% of patients who were receiving alogliptin 25 mg in combination with pioglitazone 30 mg and metformin and 22% of patients receiving a dose titration of pioglitazone from 30 mg to 45 mg in combination with metformin required glycemic rescue.

Improvements in A1C were not affected by gender, age, race or baseline BMI. The mean increase in body weight was similar in both treatment arms. Lipid effects were neutral.

Table 12. Glycemic Parameters at Week 52 in an Active-Controlled Study of Alogliptin as Add-On Combination Therapy to Metformin and Pioglitazone*		
	Alogliptin 25 mg + Pioglitazone 30 mg + Metformin	**Pioglitazone 45 mg + Metformin**
A1C (%)	N=397	N=394
Baseline (mean)	8.2	8.1
Change from Baseline (adjusted mean†)	-0.7	-0.3
Difference from Pioglitazone 45 mg + Metformin (adjusted mean† with 95% confidence interval)	-0.4‡ (-0.5, -0.3)	-
% of Patients (n/N) achieving A1C ≤7%	33% (134/404)§	21% (85/399)
FPG (mg/dL)	N=399	N=396
Baseline (mean)	162	162
Change from Baseline (adjusted mean†)	-15	-4
Difference from Pioglitazone 45 mg + Metformin (adjusted mean† with 95% confidence interval)	-11§ (-16, -6)	-

*Intent-to-treat population using last observation on study
†Least squares means adjusted for treatment, baseline value, geographic region and baseline metformin dose
‡Noninferior and statistically superior to metformin plus pioglitazone at the 0.025 one-sided significance level
§$p<0.001$ compared to pioglitazone 45 mg + metformin

Alogliptin Add-On Therapy to a Thiazolidinedione

A 26 week, placebo-controlled study, was conducted to evaluate the efficacy and safety of alogliptin as add-on therapy to pioglitazone in patients with type 2 diabetes. A total of 493 patients inadequately controlled on a thiazolidinedione alone or in combination with metformin or a sulfonylurea (mean baseline A1C=8%) were randomized to receive alogliptin 12.5 mg, alogliptin 25 mg or placebo. Patients were maintained on a stable dose of pioglitazone (median dose=30 mg) during the treatment period and those who were also previously treated on metformin (median dose=2000 mg) or sulfonylurea (median dose=10 mg) prior to randomization were maintained on the combination therapy during the treatment period. All patients entered into a four week, single-blind, placebo run-in period prior to randomization. Following randomization, all patients continued to receive instruction on diet and exercise. Patients who failed to meet prespecified hyperglycemic goals during the 26 week treatment period received glycemic rescue.

The addition of alogliptin 25 mg once daily to pioglitazone therapy resulted in significant improvements from baseline in A1C and FPG at Week 26 when compared to the addition of placebo *(Table 13)*. A total of 9% of patients who were receiving alogliptin 25 mg and 12% of patients receiving placebo required glycemic rescue.

The improvement in A1C was not affected by gender, age, baseline BMI or baseline pioglitazone dose. The mean increase in body weight was similar between alogliptin and placebo when given in combination with pioglitazone. Lipid effects were neutral.

Table 13. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of Alogliptin as Add-On Therapy to Pioglitazone*

	Alogliptin 25 mg + Pioglitazone ± Metformin ± Sulfonylurea	**Placebo + Pioglitazone ± Metformin ± Sulfonylurea**
A1C (%)	N=195	N=95
Baseline (mean)	8	8
Change from baseline (adjusted mean[†])	-0.8	-0.2
Difference from placebo (adjusted mean[†] with 95% confidence interval)	-0.6[‡] (-0.8, -0.4)	-
% of patients (n/N) achieving A1C ≤7%	49% (98/199)[‡]	34% (33/97)
FPG (mg/dL)	N=197	N=97
Baseline (mean)	170	172
Change from baseline (adjusted mean[†])	-20	-6
Difference from placebo (adjusted mean[†] with 95% confidence interval)	-14[‡] (-23, -5)	-

*Intent-to-treat population using last observation on study
[†]Least squares means adjusted for treatment, baseline value, geographic region, baseline treatment regimen (pioglitazone, pioglitazone + metformin or pioglitazone + sulfonylurea) and baseline pioglitazone dose
[‡]$p<0.01$ compared to placebo

Cardiovascular Safety Trial

A randomized, double-blind, placebo-controlled cardiovascular outcomes trial (EXAMINE) was conducted to evaluate the cardiovascular risk of alogliptin. The trial compared the risk of major adverse cardiovascular events (MACE) between alogliptin (N=2701) and placebo (N=2679) when added to standard of care therapies for diabetes and atherosclerotic vascular disease (ASCVD). The trial was event driven and patients were followed until a sufficient number of primary outcome events accrued.

Eligible patients were adults with type 2 diabetes who had inadequate glycemic control at baseline (e.g., HbA1c >6.5%) and had been hospitalized for an acute coronary syndrome event (e.g., acute

myocardial infarction or unstable angina requiring hospitalization) 15 to 90 days prior to randomization. The dose of alogliptin was based on estimated renal function at baseline per dosage and administration recommendations *[see Dosage and Administration (2.2)]*. The average time between an acute coronary syndrome event and randomization was approximately 48 days.

The mean age of the population was 61 years. Most patients were male (68%), Caucasian (73%), and were recruited from outside of the United States (86%). Asian and Black patients contributed 20% and 4% of the total population, respectively. At the time of randomization patients had a diagnosis of type 2 diabetes mellitus for approximately 9 years, 87% had a prior myocardial infarction and 14% were current smokers. Hypertension (83%) and renal impairment (27% with an eGFR ≤60 ml/min/1.73 m^2) were prevalent co-morbid conditions. Use of medications to treat diabetes (e.g., metformin 73%, sulfonylurea 54%, insulin 41%), and ASCVD (e.g., statin 94%, aspirin 93%, renin-angiotensin system blocker 88%, beta-blocker 87%) was similar between patients randomized to alogliptin and placebo at baseline. During the trial, medications to treat diabetes and ASCVD could be adjusted to ensure care for these conditions adhered to standard of care recommendations set by local practice guidelines.

The primary endpoint in EXAMINE was the time to first occurrence of a MACE defined as the composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. The study was designed to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE. The median exposure to study drug was 526 days and 95% of the patients were followed to study completion or death.

Table 14 shows the study results for the primary MACE composite endpoint and the contribution of each component to the primary MACE endpoint. The upper bound of the confidence interval was 1.16 and excluded a risk margin larger than 1.3.

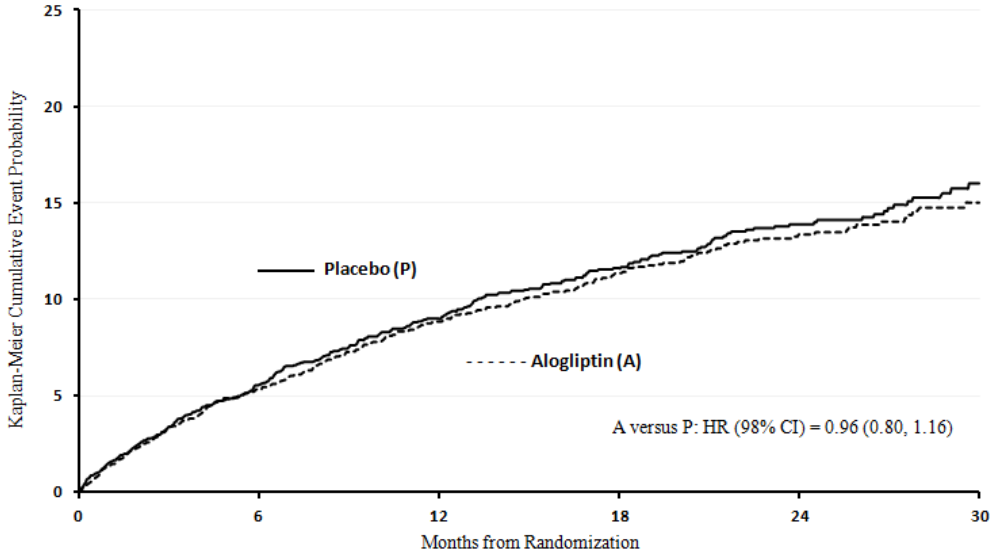
Table 14. Patients with MACE in EXAMINE

Composite of first event of CV death, nonfatal MI or nonfatal stroke (MACE)	**Alogliptin**		**Placebo**		**Hazard Ratio**
	Number of Patients (%)	**Rate per 100 PY***	**Number of Patients (%)**	**Rate per 100 PY***	**(98% CI)**
	N=2701		N=2679		
	305 (11.3)	7.6	316 (11.8)	7.9	0.96 (0.80, 1.16)
CV Death	89 (3.3)	2.2	111 (4.1)	2.8	
Nonfatal MI	187 (6.9)	4.6	173 (6.5)	4.3	
Nonfatal stroke	29 (1.1)	0.7	32 (1.2)	0.8	

*Patient Years (PY)

The Kaplan-Meier based cumulative event probability is presented in Figure 4 for the time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for placebo and alogliptin overlap throughout the duration of the study. The observed incidence of MACE was highest within the first 60 days after randomization in both treatment arms (14.8 MACE per 100 PY), decreased from day 60 to the end of the first year (8.4 per 100 PY) and was lowest after one year of follow-up (5.2 per 100 PY).

Figure 4. Observed Cumulative Rate of MACE in EXAMINE



At risk:						
A	2701	2316	1899	1394	821	296
P	2679	2299	1891	1375	805	286

The rate of all cause death was similar between treatment arms with 153 (3.6 per 100 PY) recorded among patients randomized to alogliptin and 173 (4.1 per 100 PY) among patients randomized to placebo. A total of 112 deaths (2.9 per 100 PY) among patients on alogliptin and 130 among patients on placebo (3.5 per 100 PY) were adjudicated as cardiovascular deaths.

16 HOW SUPPLIED/STORAGE AND HANDLING

OSENI tablets are available in the following strengths and packages:

25 mg/15 mg tablet: yellow, round, biconvex and film-coated with both “A/P” and “25/15” printed on one side, available in:

NDC 64764-251-03	Bottles of 30 tablets
NDC 64764-251-04	Bottles of 90 tablets
NDC 64764-251-05	Bottles of 500 tablets

25 mg/30 mg tablet: peach, round, biconvex and film-coated with both “A/P” and “25/30” printed on one side, available in:

NDC 64764-253-03	Bottles of 30 tablets
NDC 64764-253-04	Bottles of 90 tablets
NDC 64764-253-05	Bottles of 500 tablets

25 mg/45 mg tablet: red, round, biconvex, film-coated and with both “A/P” and “25/45” printed on one side, available in:

NDC 64764-254-03	Bottles of 30 tablets
NDC 64764-254-04	Bottles of 90 tablets
NDC 64764-254-05	Bottles of 500 tablets

12.5 mg/15 mg tablet: pale yellow, round, biconvex and film-coated with both “A/P” and “12.5/15” printed on one side, available in:

NDC 64764-121-03	Bottles of 30 tablets
NDC 64764-121-04	Bottles of 90 tablets
NDC 64764-121-05	Bottles of 500 tablets

12.5 mg/30 mg tablet: pale peach, round, biconvex and film-coated with both “A/P” and “12.5/30” printed on one side, available in:

NDC 64764-123-03	Bottles of 30 tablets
NDC 64764-123-04	Bottles of 90 tablets
NDC 64764-123-05	Bottles of 500 tablets

12.5 mg/45 mg tablet: pale red, round, biconvex and film-coated with both “A/P” and “12.5/45” printed on one side, available in:

NDC 64764-124-03	Bottles of 30 tablets
NDC 64764-124-04	Bottles of 90 tablets
NDC 64764-124-05	Bottles of 500 tablets

Storage
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed and protect from moisture and humidity.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the potential risks and benefits of OSENI.

Patients should be informed of the signs and symptoms of heart failure. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on OSENI should immediately report these symptoms to their physician. Before initiating OSENI, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment.

Patients should be informed that acute pancreatitis has been reported during use of alogliptin. Patients should be informed that persistent, severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue OSENI and contact their physician if persistent severe abdominal pain occurs.

Patients should be informed that allergic reactions have been reported during use of alogliptin and pioglitazone. If symptoms of allergic reactions (including skin rash, hives and swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing) occur, patients should be instructed to discontinue OSENI and seek medical advice promptly.

Patients should be informed that postmarketing reports of liver injury, sometimes fatal, have been reported during use of alogliptin and pioglitazone. If signs or symptoms of liver injury occur (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia or dark urine), patients should be instructed to discontinue OSENI and seek medical advice promptly.

Tell patients to promptly report any sign of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment, as these may be due to bladder cancer.

Inform patients that hypoglycemia can occur, particularly when an insulin secretagogue or insulin is used in combination with OSENI. Explain the risks, symptoms and appropriate management of hypoglycemia.

Inform female patients that treatment with pioglitazone, like other thiazolidinediones, may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation *[see Use in Specific Populations (8.3)]*.

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs.

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.11)]*.

Instruct patients to take OSENI only as prescribed daily. OSENI can be taken with or without meals. If a dose is missed, advise patients not to double their next dose.
Patients should be informed that the tablets must never be split.

Instruct patients to read the Medication Guide before starting OSENI therapy and to reread each time the prescription is refilled. Instruct patients to inform their healthcare provider if an unusual symptom develops or if a symptom persists or worsens.

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MEDICATION GUIDE

OSENI (OH-senn-ee)
(alogliptin and pioglitazone)
tablets

Read this Medication Guide carefully before you start taking OSENI and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about OSENI, ask your doctor or pharmacist.

What is the most important information I should know about OSENI?

OSENI can cause serious side effects, including:

1. **Heart failure:** OSENI can cause heart failure and cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure.

   Before you start taking OSENI:

   Tell your doctor if you have ever had heart failure or have problems with your kidneys.

   Call your doctor right away if you have any of the following symptoms:

   - shortness of breath or trouble breathing, especially when you lie down
   - an unusually fast increase in weight
   - swelling or fluid retention, especially in the feet, ankles, or legs

   These may be symptoms of heart failure.

2. **Inflammation of the pancreas (pancreatitis):** Alogliptin, one of the medicines in OSENI, may cause pancreatitis, which may be severe. Certain medical conditions make you more likely to get pancreatitis.

Before you start taking OSENI:

Tell your doctor if you have ever had:

- pancreatitis
- kidney problems
- liver problems

Stop taking OSENI and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is OSENI?

- OSENI contains 2 prescription diabetes medicines, alogliptin (NESINA) and pioglitazone (ACTOS).
- OSENI is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- OSENI is not for people with type 1 diabetes.
- OSENI is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if OSENI is safe and effective in children under the age of 18. OSENI is not recommended for use in children.

Who should not take OSENI?

Do not take OSENI if you:

- have severe heart failure
- are allergic to alogliptin (NESINA), pioglitazone (ACTOS) or any ingredient in OSENI or have had a serious allergic (hypersensitivity) reaction to alogliptin or pioglitazone. See the end of this Medication Guide for a complete list of the ingredients in OSENI.

Symptoms of a serious allergic reaction to OSENI may include:

- swelling of your face, lips, throat and other areas on your skin
- raised, red areas on your skin (hives)
- difficulty with swallowing or breathing
- skin rash, itching, flaking or peeling

If you have these symptoms, stop taking OSENI and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before and during treatment with OSENI?

Before you start taking OSENI, tell your doctor if you:

- have heart failure

- have a type of diabetic eye disease that causes swelling of the back of the eye (macular edema)
- have kidney or liver problems
- have or have had inflammation of the pancreas (pancreatitis)
- have or have had cancer of the bladder
- have other medical conditions
- **are pregnant or plan to become pregnant.** It is not known if OSENI can harm your unborn baby. Talk to your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant.
- **are a premenopausal woman who does not have periods regularly or at all.** OSENI may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking OSENI. Tell your doctor right away if you become pregnant while taking OSENI.
- **are breastfeeding or plan to breastfeed.** It is not known whether OSENI passes into your breast milk and if it can harm your baby. Talk with your doctor about the best way to control your blood glucose levels while breastfeeding.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist before you start a new medicine.

OSENI may affect the way other medicines work, and other medicines may affect how OSENI works. Contact your doctor before you start or stop other types of medicines.

How should I take OSENI?

- Take OSENI exactly as your doctor tells you to take it.
- Take OSENI 1 time each day with or without food.
- Do not break or cut OSENI tablets before swallowing.
- Your doctor may need to change your dose of OSENI to control your blood glucose. Do not change your dose unless told to do so by your doctor.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and take the next dose at your regular time. **Do not** take 2 doses of OSENI at the same time.
- If you take too much OSENI, call your doctor or go to the nearest hospital emergency room right away.
- If your body is under stress, such as from fever, infection, accident or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.
- Stay on your diet and exercise programs and check your blood sugar as your doctor tells you to.
- Your doctor may do certain blood tests before you start OSENI and during treatment as needed. Your doctor may change your dose of OSENI based on the results of your blood tests due to how well your kidneys are working.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor should check your eyes regularly while you take OSENI.

What are the possible side effects of OSENI?

OSENI can cause serious side effects, including:

- See **"What is the most important information I should know about OSENI?"**
- **Allergic (hypersensitivity) reactions,** such as:
  - swelling of your face, lips, throat and other areas on your skin
  - raised, red areas on your skin (hives)
  - difficulty swallowing or breathing
  - skin rash, itching, flaking or peeling

If you have these symptoms, stop taking OSENI and contact your doctor right away.

- **Liver problems.** Call your doctor right away if you have unexplained symptoms such as:
  - nausea or vomiting
  - loss of appetite
  - stomach pain
  - dark urine
  - unusual or unexplained tiredness
  - yellowing of your skin or the whites of your eyes
- **Broken bones (fractures).** Usually in the hand, upper arm or foot in women. Talk to your doctor for advice on how to keep your bones healthy.

- **Bladder cancer.** There may be an increased chance of having bladder cancer when you take OSENI. You should not take OSENI if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
  - o blood or a red color in your urine
  - o an increased need to urinate
  - o pain while you urinate
- **Low blood sugar (hypoglycemia).** If you take OSENI with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take OSENI. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your doctor. Signs and symptoms of low blood sugar may include:
  - o shaking or feeling jittery
  - o sweating
  - o fast heartbeat
  - o change in vision
  - o hunger
  - o headache
  - o change in mood
  - o confusion
  - o dizziness
- **Diabetic eye disease with swelling in the back of the eye (macular edema).** Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly.
- **Release of an egg from an ovary in a woman (ovulation) leading to pregnancy.** Ovulation may happen when premenopausal women who do not have regular monthly periods take OSENI. This can increase your chance of getting pregnant.
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in OSENI, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in OSENI, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking OSENI.

The most common side effects of OSENI include stuffy or runny nose and sore throat, back pain, cold-like symptoms (upper respiratory tract infection).

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OSENI. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OSENI?

- Store OSENI at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep container tightly closed and protect from moisture and humidity.

Keep OSENI and all medicines out of the reach of children.

General information about the safe and effective use of OSENI

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take OSENI for a condition for which it was not prescribed. Do not give OSENI to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about OSENI. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about OSENI that is written for health professionals.

For more information, go to www.oseni.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in OSENI?

Active ingredients: alogliptin and pioglitazone.

Inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, and lactose monohydrate; the tablets are film-coated with hypromellose, polyethylene glycol, titanium dioxide, talc and ferric oxide (yellow and/or red) and are marked with red A1 or gray F1 printing ink.

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