

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
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.**
- **OSENI is not recommended in patients with symptomatic heart failure.**
- **Initiation of OSENI in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. (4, 5.1)**

INDICATIONS AND USAGE

OSENI is 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)

Limitation of Use: Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.2)

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.
- 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. Monitor patients for signs and symptoms. (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. 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:** Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further suggest that the risk increases with duration of use. 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)
- **Macrovascular outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with OSENI or any other antidiabetic drug. (5.11)

ADVERSE REACTIONS

Common adverse reactions reported in ≥4% of patients treated with coadministration of alogliptin 25 mg and pioglitazone 15 mg, 30 mg or 45 mg were 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)

USE IN SPECIFIC POPULATIONS

- **Nursing mothers:** Discontinue drug or nursing, taking into consideration the importance of the drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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1 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.
- OSENI is not recommended in patients with symptomatic heart failure.
- 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)*].

2 1 INDICATIONS AND USAGE

3 1.1 Monotherapy and Combination Therapy

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

7 1.2 Limitation of Use

8 OSENI should not be used in patients with type 1 diabetes mellitus or for the treatment
9 of diabetic ketoacidosis, as it would not be effective in these settings.

10 Use with caution in patients with liver disease [see *Warnings and Precautions (5.4)*].

11 2 DOSAGE AND ADMINISTRATION

12 2.1 Recommendations for All Patients

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

15
16 The recommended starting dose for OSENI (alogliptin and pioglitazone):

- 17 • for patients inadequately controlled on diet and exercise is 25 mg/15 mg or 25
18 mg/30 mg,
- 19 • for patients inadequately controlled on metformin monotherapy is 25 mg/15 mg or
20 25 mg/30 mg,
- 21 • for patients on alogliptin who require additional glycemic control is 25 mg/15 mg or
22 25 mg/30 mg,
- 23 • for patients on pioglitazone who require additional glycemic control is 25 mg/15
24 mg, 25 mg/30 mg, or 25 mg/45 mg as appropriate based upon current therapy,

- 25 • for patients switching from alogliptin coadministered with pioglitazone, OSENI may
26 be initiated at the dose of alogliptin and pioglitazone based upon current therapy,
- 27 • for patients with congestive heart failure (NYHA Class I or II) is 25 mg/15 mg.

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

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

34 **2.2 Patients with Renal Impairment**

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

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

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

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

45 **2.3 Coadministration with Strong CYP2C8 Inhibitors**

46 Coadministration of pioglitazone and gemfibrozil, a strong CYP2C8 inhibitor, increases
47 pioglitazone exposure approximately 3-fold. Therefore, the maximum recommended
48 dose of OSENI is 25 mg/15 mg daily when used in combination with gemfibrozil or other
49 strong CYP2C8 inhibitors [see *Drug Interactions (7.1)* and *Clinical Pharmacology*
50 *(12.3)*].

51 **3 DOSAGE FORMS AND STRENGTHS**

- 52 • 25 mg/15 mg tablets are yellow, round, biconvex, film-coated, with both “A/P” and
53 “25/15” printed on one side.
- 54 • 25 mg/30 mg tablets are peach, round, biconvex, film-coated, with both “A/P” and
55 “25/30” printed on one side.
- 56 • 25 mg/45 mg tablets are red, round, biconvex, film-coated, with both “A/P” and
57 “25/45” printed on one side.
- 58 • 12.5 mg/15 mg tablets are pale yellow, round, biconvex, film-coated, with both
59 “A/P” and “12.5/15” printed on one side.
- 60 • 12.5 mg/30 mg tablets are pale peach, round, biconvex, film-coated, with both
61 “A/P” and “12.5/30” printed on one side.

- 62 • 12.5 mg/45 mg tablets are pale red, round, biconvex, film-coated, with both “A/P”
63 and “12.5/45” printed on one side.

64 **4 CONTRAINDICATIONS**

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

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

68 **5 WARNINGS AND PRECAUTIONS**

69 **5.1 Congestive Heart Failure**

70 **Pioglitazone**

71 Pioglitazone, like other thiazolidinediones, can cause dose-related fluid retention when
72 used alone or in combination with other antidiabetic medications and is most common
73 when pioglitazone is used in combination with insulin. Fluid retention may lead to or
74 exacerbate congestive heart failure. Patients should be observed for signs and
75 symptoms of congestive heart failure. If congestive heart failure develops, it should be
76 managed according to current standards of care and discontinuation or dose reduction
77 of pioglitazone must be considered [*see Boxed Warning, Contraindications (4), and*
78 *Adverse Reactions (6.1)*].

79 **5.2 Pancreatitis**

80 There have been postmarketing reports of acute pancreatitis in patients taking
81 alogliptin. After initiation of OSENI, patients should be observed carefully for signs and
82 symptoms of pancreatitis. If pancreatitis is suspected, OSENI should promptly be
83 discontinued and appropriate management should be initiated. It is unknown whether
84 patients with a history of pancreatitis are at increased risk for the development of
85 pancreatitis while using OSENI.

86 **5.3 Hypersensitivity Reactions**

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

95 **5.4 Hepatic Effects**

96 There have been postmarketing reports of fatal and non-fatal hepatic events in patients
97 taking pioglitazone or alogliptin, although the reports contain insufficient information
98 necessary to establish the probable cause [*see Adverse Reactions (6.3)*]. There has
99 been no evidence of drug-induced hepatotoxicity in the pioglitazone controlled clinical
100 trial database to date [*see Adverse Reactions (6.1)*]. In randomized controlled studies of
101 alogliptin, serum alanine aminotransferase (ALT) elevations greater than three times the

102 upper limit of normal (ULN) were observed: 1.3% in alogliptin-treated patients and 1.5%
103 in all comparator-treated patients.

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

111 Measure liver tests promptly in patients who report symptoms that may indicate liver
112 injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or
113 jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT
114 greater than 3 times the upper limit of the reference range), OSENI treatment should be
115 interrupted and an investigation done to establish the probable cause. OSENI should
116 not be restarted in these patients without another explanation for the liver test
117 abnormalities.

118 **5.5 Edema**

119 **Pioglitazone**

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

124 OSENI should be used with caution in patients with edema. Because thiazolidinediones,
125 including pioglitazone, can cause fluid retention, which can exacerbate or lead to
126 congestive heart failure, OSENI should be used with caution in patients at risk for
127 congestive heart failure. Patients treated with OSENI should be monitored for signs and
128 symptoms of congestive heart failure [see *Boxed Warning, Warnings and Precautions*
129 *(5.1)* and *Patient Counseling Information (17.1)*].

130 **5.6 Fractures**

131 **Pioglitazone**

132 In PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events),
133 5238 patients with type 2 diabetes and a history of macrovascular disease were
134 randomized to pioglitazone (N=2605), force-titrated up to 45 mg daily or placebo
135 (N=2633) in addition to standard of care. During a mean follow-up of 34.5 months, the
136 incidence of bone fracture in females was 5.1% (44/870) for pioglitazone versus 2.5%
137 (23/905) for placebo. This difference was noted after the first year of treatment and
138 persisted during the course of the study. The majority of fractures observed in female
139 patients were nonvertebral fractures including lower limb and distal upper limb. No
140 increase in the incidence of fracture was observed in men treated with pioglitazone
141 (1.7%) versus placebo (2.1%). The risk of fracture should be considered in the care of
142 patients, especially female patients, treated with pioglitazone and attention should be
143 given to assessing and maintaining bone health according to current standards of care.

144 **5.7 Urinary Bladder Tumors**

145 **Pioglitazone**

146 Tumors were observed in the urinary bladder of male rats in the two-year
147 carcinogenicity study [see *Nonclinical Toxicology* (13.1)]. In two 3-year trials in which
148 pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports
149 of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients
150 not taking pioglitazone. After excluding patients in whom exposure to study drug was
151 less than one year at the time of diagnosis of bladder cancer, there were six (0.16%)
152 cases on pioglitazone and two (0.05%) cases on placebo.

153 A five-year interim report of an ongoing 10-year observational cohort study found a
154 nonsignificant increase in the risk for bladder cancer in subjects ever exposed to
155 pioglitazone, compared to subjects never exposed to pioglitazone (HR 1.2 [95% CI 0.9–
156 1.5]). Compared to never exposure, a duration of pioglitazone therapy longer than 12
157 months was associated with an increase in risk (HR 1.4 [95% CI 0.9–2.1]), which
158 reached statistical significance after more than 24 months of pioglitazone use (HR 1.4
159 [95% CI 1.03–2.0]). Interim results from this study suggested that taking pioglitazone
160 longer than 12 months increased the relative risk of developing bladder cancer in any
161 given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from
162 approximately 7 in 10,000 [without pioglitazone] to approximately 10 in 10,000 [with
163 pioglitazone]).

164 There are insufficient data to determine whether pioglitazone is a tumor promoter for
165 urinary bladder tumors. Consequently, pioglitazone should not be used in patients with
166 active bladder cancer and the benefits of glycemic control versus unknown risks for
167 cancer recurrence with pioglitazone should be considered in patients with a prior history
168 of bladder cancer.

169 **5.8 Use with Medications Known to Cause Hypoglycemia**

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

173 **5.9 Macular Edema**

174 **Pioglitazone**

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

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

182 Patients with diabetes should have regular eye exams by an ophthalmologist according
183 to current standards of care. Patients with diabetes who report any visual symptoms

184 should be promptly referred to an ophthalmologist, regardless of the patient's underlying
185 medications or other physical findings [see *Adverse Reactions (6.1)*].

186 **5.10 Ovulation**

187 **Pioglitazone**

188 Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some
189 premenopausal anovulatory women. As a result, these patients may be at an increased
190 risk for pregnancy while taking OSENI [see *Use in Specific Populations (8.1)*]. This
191 effect has not been investigated in clinical trials, so the frequency of this occurrence is
192 not known. Adequate contraception in all premenopausal women treated with OSENI is
193 recommended.

194 **5.11 Macrovascular Outcomes**

195 There have been no clinical studies establishing conclusive evidence of macrovascular
196 risk reduction with OSENI or any other antidiabetic drug.

197 **6 ADVERSE REACTIONS**

198 **6.1 Clinical Studies Experience**

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

202 **Alogliptin and Pioglitazone**

203 Over 1500 patients with type 2 diabetes have received alogliptin coadministered with
204 pioglitazone in four large randomized, double-blind controlled clinical trials. The mean
205 exposure to OSENI was 29 weeks with more than 100 subjects treated for more than
206 one year. The studies consisted of two placebo-controlled studies of 16 to 26 weeks
207 duration and two active-controlled studies of 26 weeks and 52 weeks in duration. In the
208 OSENI arm, the mean duration of diabetes was approximately 6 years, the mean body
209 mass index (BMI) was 31 kg/m² (54% of patients had a BMI ≥30 kg/m²), and the mean
210 age was 54 years (16% of patients ≥65 years of age).

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

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

218

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

219 ***Alogliptin Add-on Therapy to a Thiazolidinedione***

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

225 **Hypoglycemia**

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

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

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

240 **Alogliptin**

241 Approximately 8500 patients with type 2 diabetes have been treated with alogliptin in 14
242 randomized, double-blind, controlled clinical trials with approximately 2900 subjects
243 randomized to placebo and approximately 2200 to an active comparator. The mean
244 exposure to alogliptin was 40 weeks with more than 2400 subjects treated for more than
245 one year. Among these patients, 63% had a history of hypertension, 51% had a history
246 of dyslipidemia, 25% had a history of myocardial infarction, 8% had a history of unstable

247 angina, and 7% had a history of congestive heart failure. The mean duration of diabetes
 248 was 7 years, the mean body mass index (BMI) was 31 kg/m² (51% of patients had a
 249 BMI ≥30 kg/m²), and the mean age was 57 years (24% of patients ≥65 years of age).

250 Two placebo-controlled monotherapy trials of 12 and 26 weeks of duration were
 251 conducted in patients treated with alogliptin 12.5 mg daily, alogliptin 25 mg daily and
 252 placebo. Four placebo-controlled add-on combination therapy trials of 26 weeks
 253 duration were also conducted: with metformin, with a sulfonylurea, with a
 254 thiazolidinedione, and with insulin.

255 Five placebo-controlled trials of 16 weeks up through two years in duration were
 256 conducted in combination with metformin, in combination with pioglitazone and with
 257 pioglitazone added to a background of metformin therapy.

258 Three active-controlled trials of 52 weeks in duration were conducted in patients treated
 259 with pioglitazone and metformin, in combination with metformin and as monotherapy
 260 compared to glipizide.

261 In a pooled analysis of these 14 controlled clinical trials, the overall incidence of adverse
 262 events was 66% in patients treated with alogliptin 25 mg compared to 62% with placebo
 263 and 70% with active comparator. Overall discontinuation of therapy due to adverse
 264 events was 4.7% with alogliptin 25 mg compared to 4.5% with placebo or 6.2% with
 265 active comparator.

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

268

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=5902	N=2926	N=2257
Nasopharyngitis	257 (4.4)	89 (3.0)	113 (5.0)
Headache	247 (4.2)	72 (2.5)	121 (5.4)
Upper respiratory tract infection	247 (4.2)	61 (2.1)	113 (5.0)

269 **Pancreatitis**

270 In the clinical trial program, pancreatitis was reported in 11 of 5902 (0.2%) patients
 271 receiving alogliptin 25 mg daily compared to 5 of 5183 (<0.1%) patients receiving all
 272 comparators.

273 **Hypersensitivity Reactions**

274 In a pooled analysis, the overall incidence of hypersensitivity reactions was 0.6% with
275 alogliptin 25 mg compared to 0.8% with all comparators. A single event of serum
276 sickness was reported in a patient treated with alogliptin 25 mg.

277 **Hypoglycemia**

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

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

286 **Pioglitazone**

287 Over 8500 patients with type 2 diabetes have been treated with pioglitazone in
288 randomized, double-blind, controlled clinical trials, including 2605 patients with type 2
289 diabetes and macrovascular disease treated with pioglitazone in the PROactive clinical
290 trial. In these trials, over 6000 patients have been treated with pioglitazone for 6 months
291 or longer, over 4500 patients have been treated with pioglitazone for one year or longer,
292 and over 3000 patients have been treated with pioglitazone for at least 2 years.

293 ***Common Adverse Events: 16- to 26-Week Monotherapy Trials***

294 A summary of the incidence and type of common adverse events reported in three
295 pooled 16- to 26-week placebo-controlled monotherapy trials of pioglitazone is provided
296 in *Table 3*. Terms that are reported represent those that occurred at an incidence of
297 >5% and more commonly in patients treated with pioglitazone than in patients who
298 received placebo. None of these adverse events were related to pioglitazone dose.

299

300

Table 3. Three Pooled 16- to 26-Week Placebo-Controlled Clinical Trials of Pioglitazone Monotherapy: Adverse Events 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

301 **Congestive Heart Failure**

302 A summary of the incidence of adverse events related to congestive heart failure for the
 303 16- to 24-week add-on to sulfonylurea trials, for the 16- to 24-week add-on to insulin
 304 trials, and for the 16- to 24-week add-on to metformin trials were (at least one
 305 congestive heart failure, 0.2% to 1.7%; hospitalized due to congestive heart failure,
 306 0.2% to 0.9%). None of the events were fatal.

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

312

313

Table 4. Treatment–Emergent Adverse Events 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%)

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

Table 5. Treatment Emergent Adverse Events 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, non-fatal	86 (3.3%)	124 (4.7%)

316 **Cardiovascular Safety**

317 In the PROactive trial, 5238 patients with type 2 diabetes and a history of
 318 macrovascular disease were randomized to pioglitazone (N=2605), force-titrated up to
 319 45 mg daily or placebo (N=2633) in addition to standard of care. Almost all patients
 320 (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors,
 321 angiotensin II receptor blockers, calcium channel blockers, nitrates, diuretics, aspirin,
 322 statins and fibrates). At baseline, patients had a mean age of 62 years, mean duration
 323 of diabetes of 9.5 years, and mean A1C of 8.1%. Mean duration of follow-up was 34.5
 324 months.

325 The primary objective of this trial was to examine the effect of pioglitazone on mortality
 326 and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high
 327 risk for macrovascular events. The primary efficacy variable was the time to the first
 328 occurrence of any event in a cardiovascular composite endpoint that included all-cause
 329 mortality, non-fatal myocardial infarction (MI) including silent MI, stroke, acute coronary
 330 syndrome, cardiac intervention including coronary artery bypass grafting or
 331 percutaneous intervention, major leg amputation above the ankle, and bypass surgery
 332 or revascularization in the leg. A total of 514 (19.7%) patients treated with pioglitazone
 333 and 572 (21.7%) placebo-treated patients experienced at least one event from the
 334 primary composite endpoint (hazard ratio 0.90; 95% Confidence Interval: 0.80, 1.02;
 335 $p=0.10$).

336 Although there was no statistically significant difference between pioglitazone and
 337 placebo for the 3-year incidence of a first event within this composite, there was no
 338 increase in mortality or in total macrovascular events with pioglitazone. The number of
 339 first occurrences and total individual events contributing to the primary composite
 340 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	
	First Events n (%)	Total Events n	First Events n (%)	Total Events n
Cardiovascular Events				
Any event	572 (21.7)	900	514 (19.7)	803
All-cause mortality	122 (4.6)	186	110 (4.2)	177
Non-fatal 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

341 Weight Gain

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

345 Edema

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

349 Hepatic Effects

350 There has been no evidence of pioglitazone-induced hepatotoxicity in the pioglitazone
351 controlled clinical trial database to date. One randomized, double-blind, 3-year trial
352 comparing pioglitazone to glyburide as add-on to metformin and insulin therapy was
353 specifically designed to evaluate the incidence of serum ALT elevation to greater than 3
354 times the upper limit of the reference range, measured every 8 weeks for the first 48
355 weeks of the trial then every 12 weeks thereafter. A total of 3/1051 (0.3%) patients
356 treated with pioglitazone and 9/1046 (0.9%) patients treated with glyburide developed
357 ALT values >3 times the upper limit of the reference range. None of the patients treated
358 with pioglitazone in the pioglitazone controlled clinical trial database to date have had a
359 serum ALT >3 times the upper limit of the reference range and a corresponding total
360 bilirubin >2 times the upper limit of the reference range, a combination predictive of the
361 potential for severe drug-induced liver injury.

362 Hypoglycemia

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

378 Urinary Bladder Tumors

379 Tumors were observed in the urinary bladder of male rats in the two-year
380 carcinogenicity study [see *Nonclinical Toxicology* (13.1)]. In two 3-year trials in which
381 pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports
382 of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients

383 not taking pioglitazone. After excluding patients in whom exposure to study drug was
384 less than one year at the time of diagnosis of bladder cancer, there were six (0.16%)
385 cases on pioglitazone and two (0.05%) cases on placebo. There are too few events of
386 bladder cancer to establish causality.

387 **6.2 Laboratory Abnormalities**

388 **Alogliptin**

389 No clinically meaningful changes in hematology, serum chemistry, or urinalysis were
390 observed in patients treated with alogliptin.

391 **Pioglitazone**

392 ***Hematologic Effects***

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

400 ***Creatine Phosphokinase***

401 During protocol-specified measurement of serum creatine phosphokinase (CPK) in
402 pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the
403 upper limit of the reference range was noted in 9 (0.2%) patients treated with
404 pioglitazone (values of 2150 to 11400 IU/L) and in no comparator-treated patient. Six of
405 these nine patients continued to receive pioglitazone, two patients were noted to have
406 the CPK elevation on the last day of dosing and one patient discontinued pioglitazone
407 due to the elevation. These elevations resolved without any apparent clinical sequelae.
408 The relationship of these events to pioglitazone therapy is unknown.

409 **6.3 Postmarketing Experience**

410 **Alogliptin**

411 The following adverse reactions have been identified during the postmarketing use of
412 alogliptin outside the United States. Because these reactions are reported voluntarily
413 from a population of uncertain size, it is not always possible to reliably estimate their
414 frequency or establish a causal relationship to drug exposure.

415 Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, and
416 severe cutaneous adverse reactions including Stevens-Johnson syndrome; hepatic
417 enzyme elevations; fulminant hepatic failure; and acute pancreatitis.

418 **Pioglitazone**

419 The following adverse reactions have been identified during the postmarketing use of
420 pioglitazone. Because these reactions are reported voluntarily from a population of
421 uncertain size, it is generally not possible to reliably estimate their frequency or
422 establish a causal relationship to drug exposure.

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

425 Fatal and non-fatal hepatic failure [see *Warnings and Precautions (5.4)*].

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

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

434 **7 DRUG INTERACTIONS**

435 **Alogliptin**

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

439 **7.1 Strong CYP2C8 Inhibitors**

440 **Pioglitazone**

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

446 **7.2 CYP2C8 Inducers**

447 **Pioglitazone**

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

453 **8 USE IN SPECIFIC POPULATIONS**

454 **8.1 Pregnancy**

455 **Pregnancy Category C**

456 **Alogliptin and Pioglitazone**

457 There are no adequate and well-controlled studies in pregnant women with OSENI or its
458 individual components. Based on animal data, the likelihood that OSENI increases the
459 risk of developmental abnormalities is predicted to be low. OSENI should be used
460 during pregnancy only if the potential benefit justifies the potential risk to the fetus.

461 When administered to rats during organogenesis the combination treatment with
462 alogliptin and pioglitazone (100 mg/kg alogliptin plus 40 mg/kg pioglitazone) slightly
463 augmented pioglitazone-related fetal effects of delayed development and reduced fetal
464 weights, but did not result in embryo-fetal mortality or teratogenicity.

465 **Alogliptin**

466 Alogliptin administered to pregnant rabbits and rats during the period of organogenesis
467 was not teratogenic at doses of up to 200 and 500 mg/kg, or 149-times and 180-times,
468 respectively, the clinical dose based on plasma drug exposure (AUC).

469 Doses of alogliptin up to 250 mg/kg (approximately 95-times clinical exposure based on
470 AUC) given to pregnant rats from gestation day 6 to lactation day 20 did not harm the
471 developing embryo or adversely affect growth and development of offspring.

472 Placental transfer of alogliptin into the fetus was observed following oral dosing to
473 pregnant rats.

474 **Pioglitazone**

475 In animal reproductive studies, pregnant rats and rabbits received pioglitazone at doses
476 up to approximately 17 (rat) and 40 (rabbit) times the MRHD based on body surface
477 area (mg/m^2); no teratogenicity was observed. Increases in embryotoxicity (increased
478 postimplantation losses, delayed development, reduced fetal weights, and delayed
479 parturition) occurred in rats that received oral doses approximately 10 or more times the
480 MRHD (mg/m^2 basis). No functional or behavioral toxicity was observed in rat offspring.
481 When pregnant rats received pioglitazone during late gestation and lactation, delayed
482 postnatal development, attributed to decreased body weight, occurred in rat offspring at
483 oral maternal doses approximately 2 or more times the MRHD (mg/m^2 basis). In rabbits,
484 embryotoxicity occurred at oral doses approximately 40 times the MRHD (mg/m^2 basis).

485 **8.3 Nursing Mothers**

486 No studies have been conducted with the combined components of OSENI. In studies
487 performed with the individual components, both alogliptin and pioglitazone are secreted
488 in the milk of lactating rats. It is not known whether alogliptin and/or pioglitazone are
489 secreted in human milk. Because many drugs are excreted in human milk, and because
490 of the potential for OSENI to cause serious adverse reactions in nursing infants, a
491 decision should be made to discontinue nursing or discontinue OSENI, taking into
492 account the importance of OSENI to the mother.

493 **8.4 Pediatric Use**

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

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

498 **8.5 Geriatric Use**

499 **Alogliptin and Pioglitazone**

500 Of the total number of patients (N=1533) in clinical safety and efficacy studies treated
501 with alogliptin and pioglitazone, 248 (16.2%) patients were 65 years and older and 15
502 (1%) patients were 75 years and older. No overall differences in safety or effectiveness
503 were observed between these patients and younger patients. While this and other
504 reported clinical experiences have not identified differences in responses between the
505 elderly and younger patients, greater sensitivity of some older individuals cannot be
506 excluded.

507 **Alogliptin**

508 Of the total number of patients (N=8507) in clinical safety and efficacy studies treated
509 with alogliptin, 2064 (24.3%) patients were 65 years and older and 341 (4%) patients
510 were 75 years and older. No overall differences in safety or effectiveness were
511 observed between patients 65 years and over and younger patients.

512 **Pioglitazone**

513 A total of 92 patients (15.2%) treated with pioglitazone in the three pooled 16- to 26-
514 week double-blind, placebo-controlled, monotherapy, trials were ≥ 65 years old and 2
515 patients (0.3%) were ≥ 75 years old. In the two pooled 16- to 24-week add-on to
516 sulfonylurea trials, 201 patients (18.7%) treated with pioglitazone were ≥ 65 years old
517 and 19 (1.8%) were ≥ 75 years old. In the two pooled 16- to 24-week add-on to
518 metformin trials, 155 patients (15.5%) treated with pioglitazone were ≥ 65 years old and
519 19 (1.9%) were ≥ 75 years old. In the two pooled 16- to 24-week add-on to insulin trials,
520 272 patients (25.4%) treated with pioglitazone were ≥ 65 years old and 22 (2.1%) were
521 ≥ 75 years old.

522 In PROactive, 1068 patients (41%) treated with pioglitazone were ≥ 65 years old and 42
523 (1.6%) were ≥ 75 years old.

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

529 **8.6 Hepatic Impairment**

530 **Alogliptin**

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

537 **Pioglitazone**

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

542 **10 OVERDOSAGE**

543 **Alogliptin**

544 The highest doses of alogliptin administered in clinical trials were single doses of 800
545 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type
546 2 diabetes (equivalent to 32 times and 16 times the maximum recommended clinical
547 dose of 25 mg, respectively). No serious adverse events were observed at these doses.

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

552 Alogliptin is minimally dialyzable; over a 3-hour hemodialysis session, approximately 7%
553 of the drug was removed. Therefore, hemodialysis is unlikely to be beneficial in an
554 overdose situation. It is not known if alogliptin is dialyzable by peritoneal dialysis.

555 **Pioglitazone**

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

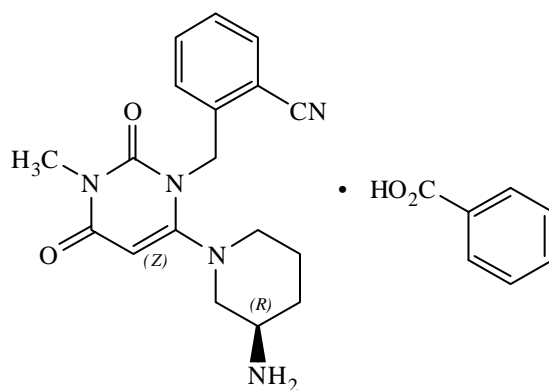
559 In the event of overdosage, appropriate supportive treatment should be initiated
560 according to patient's clinical signs and symptoms.

561 **11 DESCRIPTION**

562 OSENI tablets contain 2 oral antihyperglycemic drugs used in the management of type
563 2 diabetes: alogliptin and pioglitazone.

564 **Alogliptin**

565 Alogliptin is a selective, orally bioavailable inhibitor of the enzymatic activity of dipeptidyl
566 peptidase-4 (DPP-4). Chemically, alogliptin is prepared as a benzoate salt, which is
567 identified as 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-
568 1(2H)-yl)methyl}benzotrile monobenzoate. It has a molecular formula of
569 $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$ and a molecular weight of 461.51 daltons. The structural formula is:



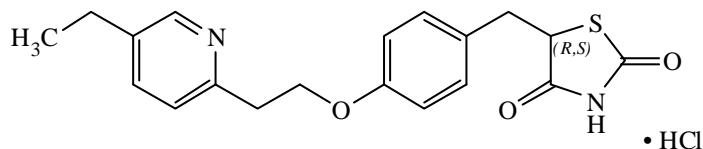
570

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

575 Pioglitazone

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

581



582

583 Pioglitazone hydrochloride is an odorless white crystalline powder that contains one
 584 asymmetric carbon in the thiazolidinedione moiety. The synthetic compound is a
 585 racemate and the two enantiomers of pioglitazone interconvert *in vivo*. It is soluble in
 586 *N,N* dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in
 587 acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

588 OSENI is available as a fixed dose combination tablet for oral administration containing
 589 34 mg alogliptin benzoate equivalent to 25 mg alogliptin and any of the following
 590 strengths of pioglitazone hydrochloride:

- 591 • 16.53 mg pioglitazone hydrochloride equivalent to 15 mg pioglitazone (25 mg/15
 592 mg) or
- 593 • 33.06 mg pioglitazone hydrochloride equivalent to 30 mg pioglitazone (25 mg/30
 594 mg) or
- 595 • 49.59 mg pioglitazone hydrochloride equivalent to 45 mg pioglitazone (25 mg/45
 596 mg).

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

- 600 • 16.53 mg pioglitazone hydrochloride equivalent to 15 mg pioglitazone (12.5 mg/15
601 mg) or
- 602 • 33.06 mg pioglitazone hydrochloride equivalent to 30 mg pioglitazone (12.5 mg/30
603 mg) or
- 604 • 49.59 mg pioglitazone hydrochloride equivalent to 45 mg pioglitazone (12.5 mg/45
605 mg).

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

611 **12 CLINICAL PHARMACOLOGY**

612 **12.1 Mechanism of Action**

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

616 **Alogliptin**

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

629 **Pioglitazone**

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

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

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

645 **12.2 Pharmacodynamics**

646 **Alogliptin and Pioglitazone**

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

660

661 **Alogliptin**

662 Single-dose administration of alogliptin to healthy subjects resulted in a peak inhibition
663 of DPP-4 within 2 to 3 hours after dosing. The peak inhibition of DPP-4 exceeded
664 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at
665 24 hours for doses greater than or equal to 25 mg. Peak and total exposure over 24
666 hours to active GLP-1 were 3- to 4-fold greater with alogliptin (at doses of 25-200 mg)
667 than placebo. In a 16-week, double-blind, placebo-controlled study alogliptin 25 mg
668 demonstrated decreases in postprandial glucagon while increasing postprandial active
669 GLP-1 levels compared to placebo over an 8 hour period following a standardized meal.
670 It is unclear how these findings relate to changes in overall glycemic control in patients
671 with type 2 diabetes mellitus. In this study, alogliptin 25 mg alone demonstrated
672 decreases in 2-hour postprandial glucose compared to placebo (-30 mg/dL versus 17.3
673 mg/dL respectively).

674 Multiple-dose administration of alogliptin to patients with type 2 diabetes also resulted in
675 a peak inhibition of DPP-4 within 1 to 2 hours and exceeded 93% across all doses (25
676 mg, 100 mg, and 400 mg) after a single dose and after 14 days of once-daily dosing). At
677 these doses of alogliptin, inhibition of DPP-4 remained above 81% at 24 hours after 14
678 days of dosing.

679 Pioglitazone

680 Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-
681 resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases
682 insulin-dependent glucose disposal, and improves hepatic sensitivity to insulin. In
683 patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone
684 results in lower plasma glucose concentrations, lower plasma insulin concentrations,
685 and lower A1C values. In controlled clinical trials, pioglitazone had an additive effect on
686 glycemic control when used in combination with a sulfonylurea, metformin, or insulin
687 [see *Clinical Studies (14)*]. Patients with lipid abnormalities were included in clinical
688 trials with pioglitazone. Overall, patients treated with pioglitazone had mean decreases
689 in serum triglycerides, mean increases in HDL cholesterol, and no consistent mean
690 changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular
691 benefit with pioglitazone or any other antidiabetic medication [see *Warnings and*
692 *Precautions (5.11) and Adverse Reactions (6.1)*].

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

699

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

700

701 In the two other monotherapy studies (16 weeks and 24 weeks) and in combination
 702 therapy studies with sulfonylurea (16 weeks and 24 weeks), metformin (16 weeks and
 703 24 weeks) or insulin (16 weeks and 24 weeks), the lipid results were generally
 704 consistent with the data above.

705 **12.3 Pharmacokinetics**

706 **Absorption and Bioavailability**

707 ***Alogliptin and Pioglitazone***

708 In bioequivalence studies of OSENI, the AUC and maximum concentration (C_{max}) of
 709 both the alogliptin and the pioglitazone component following a single dose of the
 710 combination tablet (12.5 mg/15 mg or 25 mg/45 mg) were bioequivalent to alogliptin
 711 (12.5 mg or 25 mg) concomitantly administered with pioglitazone (15 mg or 45 mg
 712 respectively) tablets under fasted conditions in healthy subjects.

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

716 **Alogliptin**

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

720 **Pioglitazone**

721 Following oral administration of pioglitazone hydrochloride, peak concentrations of
722 pioglitazone were observed within 2 hours. Food slightly delays the time to peak serum
723 concentration (T_{max}) to 3 to 4 hours, but does not alter the extent of absorption (AUC).

724 **Distribution**

725 **Alogliptin**

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

729 Alogliptin is 20% bound to plasma proteins.

730 **Pioglitazone**

731 The mean apparent V_d/F of pioglitazone following single-dose administration is $0.63 \pm$
732 0.41 (mean \pm SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%)
733 in human serum, principally to serum albumin. Pioglitazone also binds to other serum
734 proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound
735 (>98%) to serum albumin.

736 **Metabolism**

737 **Alogliptin**

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

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

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

749 **Pioglitazone**

750 Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites
751 also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are
752 the major circulating active metabolites in humans. Following once daily administration

753 of pioglitazone, steady-state serum concentrations of both pioglitazone and its major
754 active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative
755 of pioglitazone), are achieved within 7 days. At steady-state, M-III and M-IV reach
756 serum concentrations equal to or greater than that of pioglitazone. At steady-state, in
757 both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises
758 approximately 30% to 50% of the peak total pioglitazone serum concentrations
759 (pioglitazone plus active metabolites) and 20% to 25% of the total AUC.

760 Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for
761 pioglitazone and M-III and M-IV, increased proportionally with administered doses of
762 15 mg and 30 mg per day.

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

771 **Excretion and Elimination**

772 ***Alogliptin***

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

777 ***Pioglitazone***

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

783 The mean serum half-life of pioglitazone and its metabolites (M-III and M-IV) range from
784 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance,
785 CL/F, calculated to be 5 to 7 L/hr.

786 **Special Populations**

787 ***Renal Impairment***

788 **Alogliptin**

789 A single-dose, open-label study was conducted to evaluate the pharmacokinetics of
790 alogliptin 50 mg in patients with chronic renal impairment compared with healthy
791 subjects. In patients with mild renal impairment (creatinine clearance (CrCl) ≥ 60 to <90
792 mL/min), an approximate 1.2-fold increase in plasma AUC of alogliptin was observed.

793 Because increases of this magnitude are not considered clinically relevant, dose
794 adjustment for patients with mild renal impairment is not recommended.

795 In patients with moderate renal impairment (CrCl ≥ 30 to < 60 mL/min), an approximate
796 2-fold increase in plasma AUC of alogliptin was observed. To maintain similar systemic
797 exposures of OSENI to those with normal renal function, the recommended dose of
798 OSENI is 12.5 mg/15 mg, 12.5 mg/30 mg, or 12.5 mg/45 mg once daily in patients with
799 moderate renal impairment.

800 In patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min) and end-stage renal
801 disease (CrCl < 15 mL/min or requiring dialysis), and approximate 3- and 4-fold increase
802 in plasma AUC of alogliptin were observed, respectively. Dialysis removed
803 approximately 7% of the drug during a 3-hour dialysis session. OSENI is not
804 recommended for patients with severe renal impairment or ESRD. Coadministration of
805 pioglitazone and alogliptin 6.25 mg once daily based on individual requirements may be
806 considered in these patients.

807 **Pioglitazone**

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

812 ***Hepatic Impairment***

813 **Alogliptin**

814 Total exposure to alogliptin was approximately 10% lower and peak exposure was
815 approximately 8% lower in patients with moderate hepatic impairment (Child-Pugh
816 Grade B) compared to healthy subjects. The magnitude of these reductions is not
817 considered to be clinically meaningful. Patients with severe hepatic impairment (Child-
818 Pugh Grade C) have not been studied. Use caution when administering OSENI to
819 patients with liver disease [*see Use in Specific Populations (8.6) and Warnings and*
820 *Precautions (5.4)*].

821 **Pioglitazone**

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

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

830 ***Gender***

831 **Alogliptin**

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

834 Pioglitazone

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

840 Geriatric**841 Alogliptin**

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

844 Pioglitazone

845 In healthy elderly subjects, peak serum concentrations of pioglitazone and total
846 pioglitazone are not significantly different, but AUC values are approximately 21%
847 higher than those achieved in younger subjects. The mean terminal half-life values of
848 pioglitazone were also longer in elderly subjects (about 10 hours) as compared to
849 younger subjects (about 7 hours). These changes were not of a magnitude that would
850 be considered clinically relevant.

851 Pediatrics**852 Alogliptin**

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

855 Pioglitazone

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

859 Race and Ethnicity**860 Alogliptin**

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

863 Pioglitazone

864 Pharmacokinetic data among various ethnic groups are not available.

865 Drug Interactions

866 Coadministration of alogliptin 25 mg once daily with a CYP2C8 substrate, pioglitazone
867 45 mg once daily for 12 days had no clinically meaningful effects on the
868 pharmacokinetics of pioglitazone and its active metabolites.

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

872 ***Alogliptin***

873 **In Vitro Assessment of Drug Interactions**

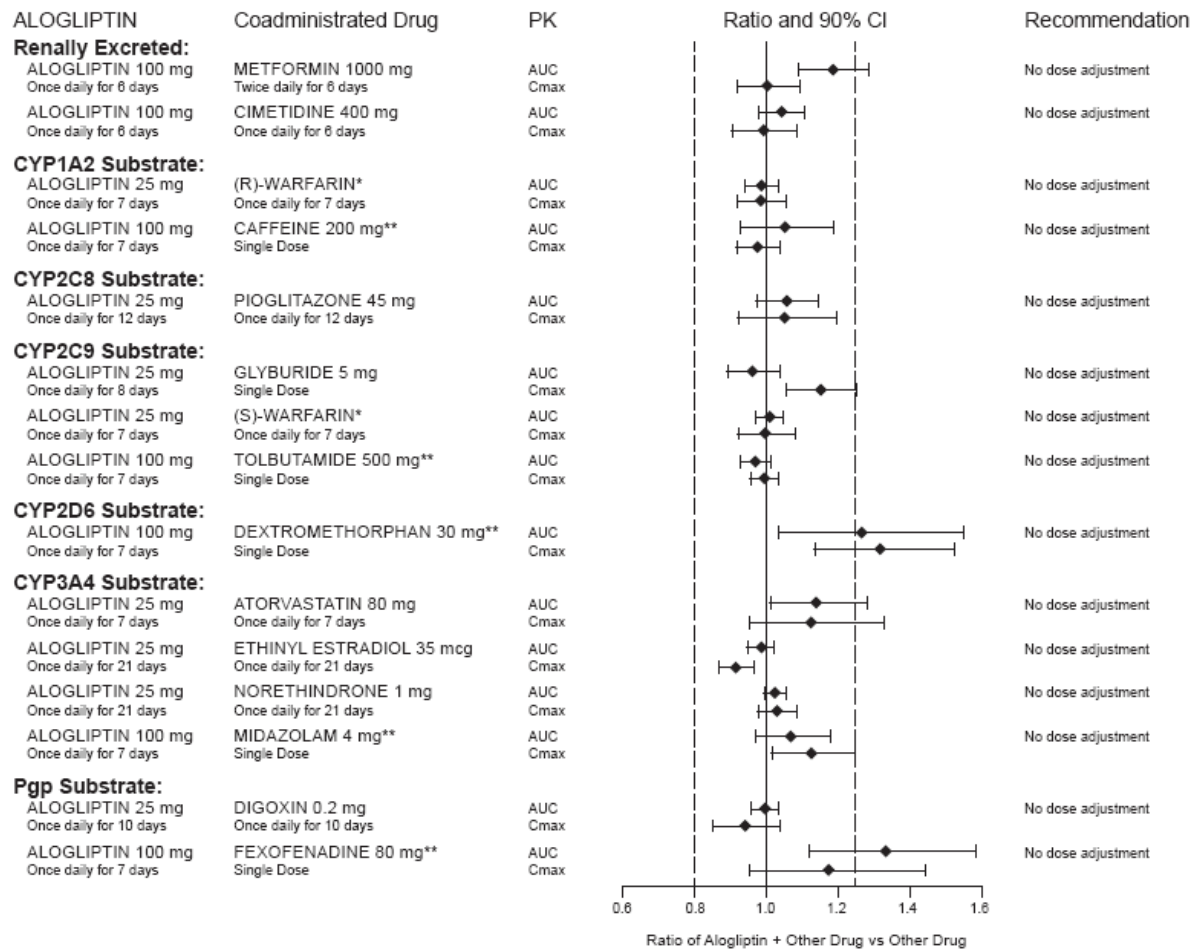
874 *In vitro* studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6,
875 CYP2C9, CYP2C19, and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9,
876 CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

877 ***In Vivo Assessment of Drug Interactions***

878 **Effects of Alogliptin on the Pharmacokinetics of Other Drugs**

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

883

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

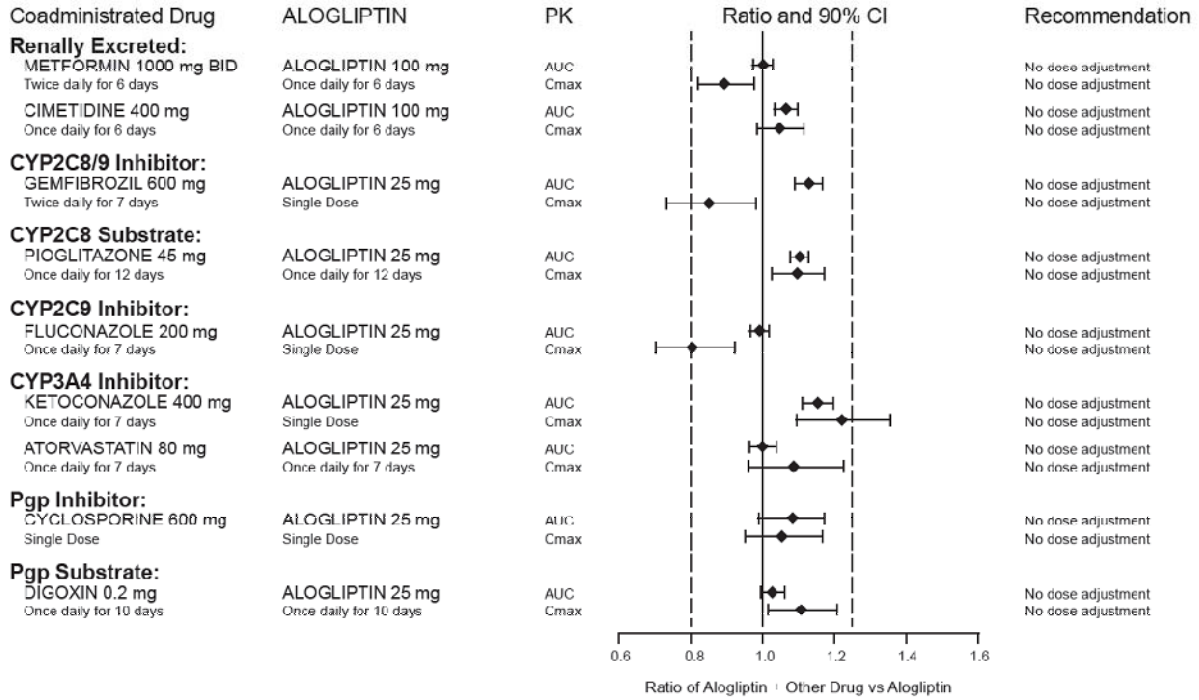
885

886 *warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no
887 significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).888 **caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam
889 (3A4 substrate), and fexofenadine (P-gp substrate) were administered as a cocktail.

890

891 **Effects of Other Drugs on the Pharmacokinetics of Alogliptin**892 There are no clinically meaningful changes in the pharmacokinetics of alogliptin when
893 alogliptin is administered concomitantly with the drugs described below (*Figure 2*).

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



895

896

897

898 Pioglitazone

Table 8. Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs					
Pioglitazone Dosage Regimen (mg)*	Coadministered Drug				
	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 7 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.

899

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%

*Daily for 7 days unless otherwise noted

[†]Mean ratio (with/without coadministered drug and no change=1-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 h to 15.1 h in the presence of gemfibrozil [see *Dosage and Administration (2.3) and Drug Interactions (7)*].

900

901

902 **13 NONCLINICAL TOXICOLOGY**

903 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

904 **Alogliptin and Pioglitazone**

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

908 **Alogliptin**

909 Rats were administered oral doses of 75, 400, and 800 mg/kg alogliptin for 2 years. No
910 drug-related tumors were observed up to 75 mg/kg or approximately 32 times the
911 maximum recommended clinical dose of 25 mg, based on AUC exposure. At higher
912 doses (approximately 308 times the maximum recommended clinical dose of 25 mg), a
913 combination of thyroid C-cell adenomas and carcinomas increased in male but not
914 female rats. No drug-related tumors were observed in mice after administration of 50,
915 150, or 300 mg/kg alogliptin for 2 years, or up to approximately 51-times the maximum
916 recommended clinical dose of 25 mg, based on AUC exposure.

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

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

923 **Pioglitazone**

924 A two year carcinogenicity study was conducted in male and female rats at oral doses
925 up to 63 mg/kg (approximately 14 times the MRHD of 45 mg based on mg/m²). Drug-
926 induced tumors were not observed in any organ except for the urinary bladder. Benign
927 and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg and
928 above (approximately equal to the MRHD based on mg/m²). A two year carcinogenicity
929 study was conducted in male and female mice at oral doses up to 100 mg/kg
930 (approximately 11 times the MRHD based on mg/m²). No drug-induced tumors were
931 observed in any organ.

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

936 No adverse effects upon fertility were observed in male and female rats at oral doses up
937 to 40 mg/kg pioglitazone daily prior to and throughout mating and gestation
938 (approximately 9 times the MRHD based on mg/m²).

939 **13.2 Animal Toxicology and/or Pharmacology**

940 **Pioglitazone**

941 Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above)
942 and dogs (3 mg/kg) treated orally with pioglitazone (approximately 11, 1, and 2 times
943 the MRHD for mice, rats, and dogs, respectively, based on mg/m²). In a one-year rat
944 study, drug-related early death due to apparent heart dysfunction occurred at an oral
945 dose of 160 mg/kg (approximately 35 times the MRHD based on mg/m²). Heart
946 enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and
947 above (approximately 4 times the MRHD based on mg/m²), but not in a 52-week study
948 at oral doses up to 32 mg/kg (approximately 13 times the MRHD based on mg/m²).

949 **14 CLINICAL STUDIES**

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

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

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

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

964 In a 26-week, double-blind, active-controlled study, a total of 655 patients inadequately
965 controlled on diet and exercise alone (mean baseline A1C = 8.8%) were randomized to
966 receive alogliptin 25 mg alone, pioglitazone 30 mg alone, alogliptin 12.5 mg with
967 pioglitazone 30 mg, or alogliptin 25 mg with pioglitazone 30 mg once daily.
968 Coadministration of alogliptin 25 mg with pioglitazone 30 mg resulted in statistically
969 significant improvements from baseline in A1C and FPG compared to either alogliptin
970 25 mg alone or to pioglitazone 30 mg alone (*Table 10*). Coadministration of alogliptin 25
971 mg with pioglitazone 30 mg once daily resulted in statistically significant reductions in
972 fasting plasma glucose (FPG) starting from Week 2 through Week 26 compared to
973 either alogliptin 25 mg or pioglitazone 30 mg alone. A total of 3% of patients receiving
974 alogliptin 25 mg coadministered with pioglitazone 30 mg, 11% of those receiving
975 alogliptin 25 mg alone, and 6% of those receiving pioglitazone 30 mg alone required
976 glycemic rescue.

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

978 The mean increase in body weight was similar between pioglitazone alone and
979 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) [‡]
Fasting Plasma Glucose (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.

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

982 In the second 26-week double-blind, placebo-controlled study, a total of 1554 patients
 983 already on metformin (mean baseline A1C=8.5%) were randomized to one of 12
 984 double-blind treatment groups: placebo; 12.5 mg or 25 mg of alogliptin alone; 15 mg, 30
 985 mg, or 45 mg of pioglitazone alone; or 12.5 mg or 25 mg of alogliptin in combination

986 with 15 mg, 30 mg, or 45 mg of pioglitazone. Patients were maintained on a stable dose
987 of metformin (median dose=1700 mg) during the treatment period. Coadministration of
988 alogliptin and pioglitazone provided statistically significant improvements in A1C and
989 FPG compared to placebo, to alogliptin alone, or to pioglitazone alone when added to
990 background metformin therapy (*Table 11, Figure 3*). A total of 4%, 5%, or 2% of patients
991 receiving alogliptin 25 mg with 15 mg, 30 mg, or 45 mg pioglitazone, 33% of patients
992 receiving placebo, 13% of patients receiving alogliptin 25 mg, and 10%, 15%, or 9% of
993 patients receiving pioglitazone 15 mg, 30 mg, or 45 mg alone required glycemic rescue.

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

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

997

998

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)‡
Fasting Plasma Glucose (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)

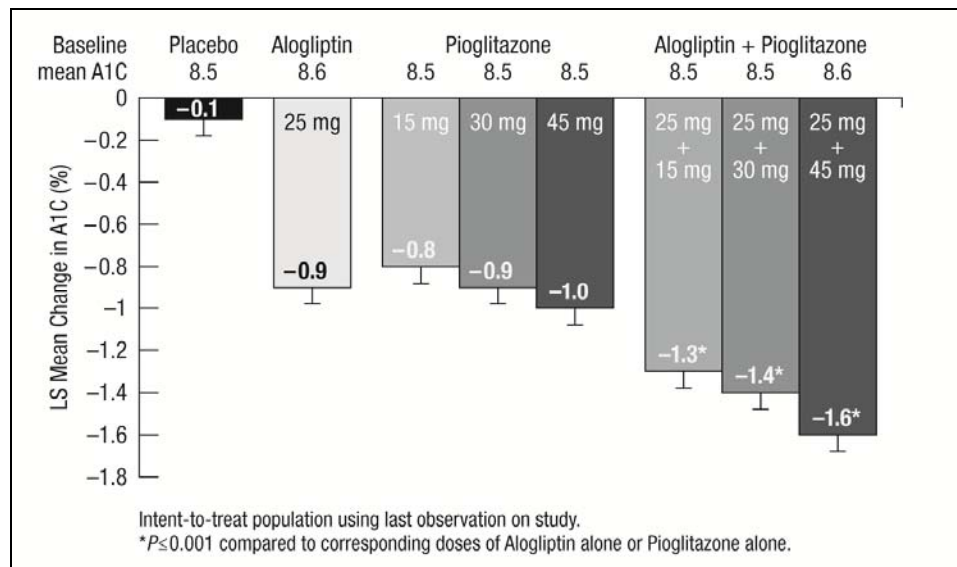
*Intent-to-treat population using last observation carried forward.

†Least squares means adjusted for treatment, geographic region, metformin dose and baseline value.

‡p≤0.01 when compared to pioglitazone and alogliptin alone.

999

1000 **Figure 3. Change From Baseline in A1C at Week 26 with Alogliptin and**
 1001 **Pioglitazone Alone and Alogliptin in Combination with Pioglitazone**
 1002 **when Added to Metformin**
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 1005

1006 **Alogliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately**
 1007 **Controlled on Metformin in Combination with Pioglitazone**

1008 In a 52-week, active-comparator study, a total of 803 patients inadequately controlled
 1009 (mean baseline A1C = 8.2%) on a current regimen of pioglitazone 30 mg and metformin
 1010 at least 1500 mg per day or at the maximum tolerated dose were randomized to either
 1011 receive the addition of alogliptin 25 mg or the titration of pioglitazone 30 mg to 45 mg
 1012 following a 4-week single-blind, placebo run-in period. Patients were maintained on a
 1013 stable dose of metformin (median dose = 1700 mg). Patients who failed to meet pre-
 1014 specified hyperglycemic goals during the 52-week treatment period received glycemic
 1015 rescue therapy.

1016 In combination with pioglitazone and metformin, alogliptin 25 mg was shown to be
 1017 statistically superior in lowering A1C and FPG compared with the titration of
 1018 pioglitazone from 30 mg to 45 mg at Week 26 at Week 52 (*Table 12, results shown only*
 1019 *for Week 52*). A total of 11% of patients who were receiving alogliptin 25 mg in
 1020 combination with pioglitazone 30 mg and metformin and 22% of patients receiving a
 1021 dose titration of pioglitazone from 30 mg to 45 mg in combination with metformin
 1022 required glycemic rescue.

1023 Improvements in A1C were not affected by gender, age, race, or baseline BMI. The
 1024 mean increase in body weight was similar in both treatment arms. Lipid effects were
 1025 neutral.

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1027

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.

‡Non-inferior and statistically superior to metformin plus pioglitazone at the 0.025 1-sided significance level.

§ p<0.001 compared to pioglitazone 45 mg + metformin.

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1030 **Alogliptin Add-on Therapy to a Thiazolidinedione**

1031 A 26-week, placebo-controlled study, was conducted to evaluate the efficacy and safety
1032 of alogliptin as add-on therapy to pioglitazone in patients with type 2 diabetes. A total of
1033 493 patients inadequately controlled on a thiazolidinedione alone or in combination with
1034 metformin or a sulfonylurea (mean baseline A1C = 8%) were randomized to receive
1035 alogliptin 12.5 mg, alogliptin 25 mg, or placebo. Patients were maintained on a stable
1036 dose of pioglitazone (median dose = 30 mg) during the treatment period and those who
1037 were also previously treated on metformin (median dose = 2000 mg) or sulfonylurea
1038 (median dose = 10 mg) prior to randomization were maintained on the combination
1039 therapy during the treatment period. All patients entered into a 4-week single-blind,
1040 placebo run-in period prior to randomization. Following randomization, all patients
1041 continued to receive instruction on diet and exercise. Patients who failed to meet pre-
1042 specified hyperglycemic goals during the 26-week treatment period received glycemic
1043 rescue.

1044 The addition of alogliptin 25 mg once daily to pioglitazone therapy resulted in significant
1045 improvements from baseline in A1C and FPG at Week 26, when compared to the
1046 addition of placebo (*Table 13*). A total of 9% of patients who were receiving alogliptin
1047 25 mg and 12% of patients receiving placebo required glycemic rescue.

1048 The improvement in A1C was not affected by gender, age, baseline BMI, or baseline
1049 pioglitazone dose. The mean increase in body weight was similar between alogliptin
1050 and placebo when given in combination with pioglitazone. Lipid effects were neutral.

1051

1052

Table 13. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of Alogliptin as Add-On Therapy to Pioglitazone*		
	Alogliptin 25 mg + Pioglitazone	Placebo + Pioglitazone
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 plus metformin, or pioglitazone plus sulfonylurea), and baseline pioglitazone dose.

[‡]p<0.01 compared to placebo.

1053 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1054 OSENI tablets are available in the following strengths and packages:

1055 25 mg/15 mg tablet: yellow, round, biconvex, film-coated, with both “A/P” and “25/15”
1056 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

1057 25 mg/30 mg tablet: peach, round, biconvex, film-coated, with both “A/P” and “25/30”
1058 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

1059 25 mg/45 mg tablet: red, round, biconvex, film-coated, with both “A/P” and “25/45”
1060 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

1061 12.5 mg/15 mg tablet: pale yellow, round, biconvex, film-coated, with both “A/P” and
1062 “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

1063 12.5 mg/30 mg tablet: pale peach, round, biconvex, film-coated, with both “A/P” and
1064 “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

1065 12.5 mg/45 mg tablet: pale red, round, biconvex, film-coated, with both “A/P” and
1066 “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

1067 **Storage**

1068 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59°- 86°F) [see USP
1069 Controlled Room Temperature]. Keep container tightly closed and protect from moisture
1070 and humidity.

1071

1072 **17 PATIENT COUNSELING INFORMATION**

1073 See FDA-Approved Patient Labeling (Medication Guide).

1074 **17.1 Instructions**

1075 Inform patients of the potential risks and benefits of OSENI.

1076 Patients who experience an unusually rapid increase in weight or edema or who
1077 develop shortness of breath or other symptoms of heart failure while on OSENI should
1078 immediately report these symptoms to their physician.

1079 Patients should be informed that acute pancreatitis has been reported during use of
1080 alogliptin. Patients should be informed that persistent, severe abdominal pain,
1081 sometimes radiating to the back, which may or may not be accompanied by vomiting, is
1082 the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly
1083 discontinue OSENI and contact their physician if persistent severe abdominal pain
1084 occurs.

1085 Patients should be informed that allergic reactions have been reported during use of
1086 alogliptin and pioglitazone. If symptoms of allergic reactions (including skin rash, hives,
1087 and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or
1088 swallowing) occur, patients should be instructed to discontinue OSENI and seek
1089 medical advice promptly.

1090 Patients should be informed that postmarketing reports of liver injury, sometimes fatal,
1091 have been reported during use of alogliptin and pioglitazone. If signs or symptoms of
1092 liver injury occur (e.g. unexplained nausea, vomiting, abdominal pain, fatigue, anorexia,
1093 or dark urine), patients should be instructed to discontinue OSENI and seek medical
1094 advice promptly.

1095 Tell patients to promptly report any sign of macroscopic hematuria or other symptoms
1096 such as dysuria or urinary urgency that develop or increase during treatment as these
1097 may be due to bladder cancer.

1098 Inform patients that hypoglycemia can occur, particularly when an insulin secretagogue
1099 or insulin is used in combination with OSENI. Explain the risks, symptoms, and
1100 appropriate management of hypoglycemia.

1101 Therapy with thiazolidinediones, including pioglitazone which is one of the active
1102 components of OSENI, may result in ovulation in some premenopausal anovulatory
1103 women. As a result, these patients may be at an increased risk for pregnancy while
1104 taking OSENI. Therefore, adequate contraception should be recommended for all
1105 premenopausal women who are prescribed OSENI.

1106 Instruct patients to take OSENI only as prescribed daily. OSENI can be taken with or
1107 without meals. If a dose is missed, advise patients not to double their next dose.

1108 Patients should be informed that the tablets must never be split.

1109 Instruct patients to read the Medication Guide before starting OSENI therapy and to
1110 reread each time the prescription is refilled. Instruct patients to inform their healthcare
1111 provider if an unusual symptom develops or if a symptom persists or worsens.

1112 Distributed by:

1113 **Takeda Pharmaceuticals America, Inc.**

1114 Deerfield, IL 60015

1115 Revised: January 2013

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1122 **MEDICATION GUIDE**

1123

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. New or worse heart failure:** Pioglitazone, one of the medicines in OSENI, can 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. Heart failure means your heart does not pump blood well enough.
 - Do not take OSENI if you have severe heart failure.
 - If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, OSENI may not be right for you.

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

- swelling or fluid retention, especially in the ankles or legs
 - shortness of breath or trouble breathing, especially when you lie down
 - an unusually fast increase in weight
 - unusual tiredness
- 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
- stones in your gallbladder (gallstones)
- a history of alcoholism
- 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 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
- difficulty with swallowing or breathing
- raised, red areas on your skin (hives)
- 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. You should not take OSENI if you breastfeed your baby. Talk with your doctor about the best way to feed your baby if you are taking OSENI.

Tell your doctor about all the medicines you take, including prescription and non-prescription 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
 - difficulty with swallowing or breathing
 - raised, red areas on your skin (hives)
 - 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
 - stomach pain
 - unusual or unexplained tiredness
 - loss of appetite
 - dark urine
 - 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:
 - blood or a red color in your urine
 - an increased need to urinate
 - 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, and then call your doctor. Signs and symptoms of low blood sugar may include:
 - shaking or feeling jittery
 - sweating
 - fast heartbeat
 - change in vision
 - hunger
 - headache
 - change in mood
 - confusion
 - 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.

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 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, ferric oxide (yellow and/or red), and are marked with red A1 or gray F1 printing ink.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:

Takeda Pharmaceuticals America, Inc.

Deerfield, IL 60015

Revised: January 2013

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