

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NESINA safely and effectively. See full prescribing information for NESINA.

**NESINA (alogliptin) tablets**  
Initial U.S. Approval: 2013

### INDICATIONS AND USAGE

NESINA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1, 14)

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

### DOSAGE AND ADMINISTRATION

- The recommended dose in patients with normal renal function or mild renal impairment is 25 mg once daily. (2.1)
- Can be taken with or without food. (2.1)
- Adjust dose if moderate or severe renal impairment or end-stage renal disease (ESRD). (2.2)

Degree of Renal Impairment	Creatinine Clearance (mL/min)	Recommended Dosing
Moderate	≥30 to <60	12.5 mg once daily
Severe/ESRD	<30	6.25 mg once daily

### DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg, 12.5 mg and 6.25 mg (3)

### CONTRAINDICATIONS

History of a serious hypersensitivity reaction to alogliptin-containing products, such as anaphylaxis, angioedema or severe cutaneous adverse reactions. (4)

### WARNINGS AND PRECAUTIONS

- Acute pancreatitis: There have been postmarketing reports of acute pancreatitis. If pancreatitis is suspected, promptly discontinue NESINA. (5.1)
- Hypersensitivity: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with NESINA such as anaphylaxis, angioedema and severe cutaneous adverse reactions. In such cases, promptly discontinue NESINA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.2)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt NESINA and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart NESINA if liver injury is confirmed and no alternative etiology can be found. (5.3)
- Hypoglycemia: When an insulin secretagogue (e.g. sulfonylurea) or insulin is used in combination with NESINA, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.4)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with NESINA or any other antidiabetic drug. (5.5)

### ADVERSE REACTIONS

Common adverse reactions (reported in ≥4% of patients treated with NESINA 25 mg and more frequently than in patients who received placebo) are: nasopharyngitis, headache, 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2013

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## 1 FULL PRESCRIBING INFORMATION

### 2 1 INDICATIONS AND USAGE

#### 3 1.1 Monotherapy and Combination Therapy

4 NESINA 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 [see *Clinical Studies*  
6 (14)].

#### 7 1.2 Limitation of Use

8 NESINA 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 2 DOSAGE AND ADMINISTRATION

#### 11 2.1 Recommended Dosing

12 The recommended dose of NESINA is 25 mg once daily.

13 NESINA may be taken with or without food.

#### 14 2.2 Patients with Renal Impairment

15 No dose adjustment of NESINA is necessary for patients with mild renal impairment  
16 (creatinine clearance [CrCl]  $\geq 60$  mL/min).

17 The dose of NESINA is 12.5 mg once daily for patients with moderate renal impairment  
18 (CrCl  $\geq 30$  to  $< 60$  mL/min).

19 The dose of NESINA is 6.25 mg once daily for patients with severe renal impairment  
20 (CrCl  $\geq 15$  to  $< 30$  mL/min) or with end-stage renal disease (ESRD) (CrCl  $< 15$  mL/min or  
21 requiring hemodialysis). NESINA may be administered without regard to the timing of  
22 dialysis. NESINA has not been studied in patients undergoing peritoneal dialysis [see  
23 *Clinical Pharmacology* (12.3)].

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

### 27 3 DOSAGE FORMS AND STRENGTHS

- 28 • 25 mg tablets are light red, oval, biconvex, film-coated, with “TAK ALG-25” printed  
29 on one side.
- 30 • 12.5 mg tablets are yellow, oval, biconvex, film-coated, with “TAK ALG-12.5”  
31 printed on one side.
- 32 • 6.25 mg tablets are light pink, oval, biconvex, film-coated, with “TAK ALG-6.25”  
33 printed on one side.

### 34 4 CONTRAINDICATIONS

35 History of a serious hypersensitivity reaction to alogliptin-containing products, such as  
36 anaphylaxis, angioedema or severe cutaneous adverse reactions.

## 37 **5 WARNINGS AND PRECAUTIONS**

### 38 **5.1 Pancreatitis**

39 There have been postmarketing reports of acute pancreatitis in patients taking NESINA.  
40 After initiation of NESINA, patients should be observed carefully for signs and  
41 symptoms of pancreatitis. If pancreatitis is suspected, NESINA should promptly be  
42 discontinued and appropriate management should be initiated. It is unknown whether  
43 patients with a history of pancreatitis are at increased risk for the development of  
44 pancreatitis while using NESINA.

### 45 **5.2 Hypersensitivity Reactions**

46 There have been postmarketing reports of serious hypersensitivity reactions in patients  
47 treated with NESINA. These reactions include anaphylaxis, angioedema, and severe  
48 cutaneous adverse reactions including Stevens-Johnson syndrome. If a serious  
49 hypersensitivity reaction is suspected, discontinue NESINA, assess for other potential  
50 causes for the event, and institute alternative treatment for diabetes [see *Adverse*  
51 *Reactions (6.2)*]. Use caution in a patient with a history of angioedema with another  
52 DPP-4 inhibitor because it is unknown whether such patients will be predisposed to  
53 angioedema with NESINA.

### 54 **5.3 Hepatic Effects**

55 There have been postmarketing reports of fatal and non-fatal hepatic failure in patients  
56 taking NESINA, although some of the reports contain insufficient information necessary  
57 to establish the probable cause [see *Adverse Reactions (6.2)*]. In randomized controlled  
58 studies, serum alanine aminotransferase (ALT) elevations greater than three times the  
59 upper limit of normal (ULN) were observed: 1.3% in alogliptin-treated patients and 1.5%  
60 in all comparator-treated patients.

61 Patients with type 2 diabetes may have fatty liver disease which may cause liver test  
62 abnormalities, and they may also have other forms of liver disease, many of which can  
63 be treated or managed. Therefore, obtaining a liver test panel and assessing the patient  
64 before initiating NESINA therapy is recommended. In patients with abnormal liver tests,  
65 NESINA should be initiated with caution.

66 Measure liver tests promptly in patients who report symptoms that may indicate liver  
67 injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or  
68 jaundice. In this clinical context, if the patient is found to have clinically significant liver  
69 enzyme elevations and if abnormal liver tests persist or worsen, NESINA should be  
70 interrupted and investigation done to establish the probable cause. NESINA should not  
71 be restarted in these patients without another explanation for the liver test  
72 abnormalities.

### 73 **5.4 Use with Medications Known to Cause Hypoglycemia**

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

### 77 **5.5 Macrovascular Outcomes**

78 There have been no clinical studies establishing conclusive evidence of macrovascular  
79 risk reduction with NESINA or any other antidiabetic drug.

## 80 **6 ADVERSE REACTIONS**

### 81 **6.1 Clinical Studies Experience**

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

85 Approximately 8500 patients with type 2 diabetes have been treated with NESINA in 14  
86 randomized, double-blind, controlled clinical trials with approximately 2900 subjects  
87 randomized to placebo and approximately 2200 to an active comparator. The mean  
88 exposure to NESINA was 40 weeks with more than 2400 subjects treated for more than  
89 one year. Among these patients, 63% had a history of hypertension, 51% had a history  
90 of dyslipidemia, 25% had a history of myocardial infarction, 8% had a history of unstable  
91 angina, and 7% had a history of congestive heart failure. The mean duration of diabetes  
92 was 7 years, the mean body mass index (BMI) was 31 kg/m<sup>2</sup> (51% of patients had a  
93 BMI ≥30 kg/m<sup>2</sup>), and the mean age was 57 years (24% of patients ≥65 years of age).

94 Two placebo-controlled monotherapy trials of 12 and 26 weeks of duration were  
95 conducted in patients treated with NESINA 12.5 mg daily, NESINA 25 mg daily and  
96 placebo. Four placebo-controlled add-on combination therapy trials of 26 weeks  
97 duration were also conducted: with metformin, with a sulfonylurea, with a  
98 thiazolidinedione, and with insulin.

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

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

105 In a pooled analysis of these 14 controlled clinical trials, the overall incidence of adverse  
106 events was 66% in patients treated with NESINA 25 mg compared to 62% with placebo  
107 and 70% with active comparator. Overall discontinuation of therapy due to adverse  
108 events was 4.7% with NESINA 25 mg compared to 4.5% with placebo or 6.2% with  
109 active comparator.

110 Adverse reactions reported in ≥4% of patients treated with NESINA 25 mg and more  
111 frequently than in patients who received placebo are summarized in *Table 1*.

112

113

<b>Table 1. Adverse Reactions Reported in ≥4% Patients Treated with NESINA 25 mg and More Frequently Than in Patients Given Placebo in Pooled Studies</b>			
	<b>Number of Patients (%)</b>		
	<b>NESINA 25 mg</b>	<b>Placebo</b>	<b>Active Comparator</b>
	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)

114

**Pancreatitis**

115 In the clinical trial program, pancreatitis was reported in 11 of 5902 (0.2%) patients  
 116 receiving NESINA 25 mg daily compared to 5 of 5183 (<0.1%) patients receiving all  
 117 comparators.

118

**Hypersensitivity Reactions**

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

122

**Hypoglycemia**

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

125

126 In the monotherapy study, the incidence of hypoglycemia was 1.5% in patients  
 127 treated with NESINA compared to 1.6% with placebo. The use of NESINA as add-on  
 128 therapy to glyburide or insulin did not increase the incidence of hypoglycemia  
 129 compared to placebo. In a monotherapy study comparing NESINA to a sulfonylurea  
 130 in elderly patients, the incidence of hypoglycemia was 5.4% with NESINA compared  
 to 26% with glipizide (*Table 2*).

131

<b>Table 2. Incidence and Rate of Hypoglycemia* in Placebo and Active-Controlled Studies when NESINA was Used as Add-on Therapy to Glyburide, Insulin, Metformin, Pioglitazone, or Compared to Glipizide</b>		
<b>Add-on to Glyburide (26 Weeks)</b>	<b>NESINA 25 mg + Glyburide</b>	<b>Placebo + Glyburide</b>
	N=198	N=99
Overall (%)	19 (9.6)	11 (11.1)
Severe (%) <sup>†</sup>	0	1 (1)
<b>Add-on to Insulin (+/- Metformin) (26 Weeks)</b>	<b>NESINA 25 mg + Insulin (+/- Metformin)</b>	<b>Placebo + Insulin (+/- Metformin)</b>
	N=129	N=129
Overall (%)	35 (27)	31 (24)
Severe (%) <sup>†</sup>	1 (0.8)	2 (1.6)
<b>Add-on to Metformin (26 Weeks)</b>	<b>NESINA 25 mg + Metformin</b>	<b>Placebo + Metformin</b>
	N=207	N=104
Overall (%)	0	3 (2.9)
Severe (%) <sup>†</sup>	0	0
<b>Add-on to Pioglitazone (± Metformin or Sulfonylurea) (26 Weeks)</b>	<b>NESINA 25 mg + Pioglitazone</b>	<b>Placebo + Pioglitazone</b>
	N=199	N=97
Overall (%)	14 (7.0)	5 (5.2)
Severe (%) <sup>†</sup>	0	1 (1)
<b>Compared to Glipizide (52 Weeks)</b>	<b>NESINA 25 mg</b>	<b>Glipizide</b>
	N=222	N=219
Overall (%)	12 (5.4)	57 (26)
Severe (%) <sup>†</sup>	0	3 (1.4)
<b>Add on to Metformin (26 Weeks)</b>	<b>NESINA 25 mg</b>	<b>Metformin 500 mg twice daily</b>
	N=112	N=109

Overall (%)	2 (1.8)	2 (1.8)
Severe (%) <sup>†</sup>	0	0
<b>Add on to Metformin Compared to Glipizide (52 Weeks)</b>	<b>NESINA 25 mg + Metformin</b>	<b>Glipizide + Metformin</b>
	N=877	N=869
Overall (%)	12 (1.4)	207 (23.8)
Severe (%) <sup>†</sup>	0	4 (0.5)

\*Adverse reactions of hypoglycemia were based on all reports of symptomatic and asymptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.

<sup>†</sup>Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level or loss of consciousness or seizure.

## 132 **Vital Signs**

133 No clinically meaningful changes in vital signs or in electrocardiograms were observed  
134 in patients treated with NESINA.

## 135 **Laboratory Tests**

136 No clinically meaningful changes in hematology, serum chemistry, or urinalysis were  
137 observed in patients treated with NESINA.

## 138 **6.2 Postmarketing Experience**

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

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

## 146 **7 DRUG INTERACTIONS**

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

## 150 **8 USE IN SPECIFIC POPULATIONS**

### 151 **8.1 Pregnancy**

#### 152 *Pregnancy Category B*

153 No adequate or well-controlled studies in pregnant women have been conducted with  
154 NESINA. Based on animal data, NESINA is not predicted to increase the risk of  
155 developmental abnormalities. Because animal reproduction studies are not always

156 predictive of human risk and exposure, NESINA, like other antidiabetic medications,  
157 should be used during pregnancy only if clearly needed.

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

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

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

### 166 **8.3 Nursing Mothers**

167 Alogliptin is secreted in the milk of lactating rats in a 2:1 ratio to plasma. It is not known  
168 whether alogliptin is excreted in human milk. Because many drugs are excreted in  
169 human milk, caution should be exercised when NESINA is administered to a nursing  
170 woman.

### 171 **8.4 Pediatric Use**

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

### 173 **8.5 Geriatric Use**

174 Of the total number of patients (N=8507) in clinical safety and efficacy studies treated  
175 with NESINA, 2064 (24.3%) patients were 65 years and older and 341 (4%) patients  
176 were 75 years and older. No overall differences in safety or effectiveness were  
177 observed between patients 65 years and over and younger patients. While this clinical  
178 experience has not identified differences in responses between the elderly and younger  
179 patients, greater sensitivity of some older individuals cannot be ruled out.

### 180 **8.6 Hepatic Impairment**

181 No dose adjustments are required in patients with mild to moderate hepatic impairment  
182 (Child-Pugh Grade A and B) based on insignificant change in systemic exposures (e.g.,  
183 AUC) compared to subjects with normal hepatic function in a pharmacokinetic study.  
184 NESINA has not been studied in patients with severe hepatic impairment (Child-Pugh  
185 Grade C). Use caution when administering NESINA to patients with liver disease [see  
186 *Warnings and Precautions (5.3)*].

## 187 **10 OVERDOSAGE**

188 The highest doses of NESINA administered in clinical trials were single doses of 800  
189 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type  
190 2 diabetes (equivalent to 32 times and 16 times the maximum recommended clinical  
191 dose of 25 mg, respectively). No serious adverse events were observed at these doses.

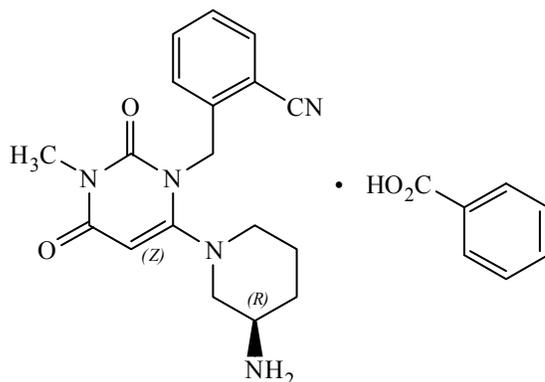
192 In the event of an overdose, it is reasonable to institute the necessary clinical monitoring  
193 and supportive therapy as dictated by the patient's clinical status. Per clinical judgment,  
194 it may be reasonable to initiate removal of unabsorbed material from the gastrointestinal  
195 tract.

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

## 199 11 DESCRIPTION

200 NESINA tablets contain the active ingredient alogliptin, which is a selective, orally-  
 201 bioavailable inhibitor of the enzymatic activity of dipeptidyl peptidase-4 (DPP-4).

202 Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[(3*R*)-3-  
 203 aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-  
 204 yl)methyl}benzonitrile monobenzoate. It has a molecular formula of  $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$   
 205 and a molecular weight of 461.51 daltons. The structural formula is:



206  
 207 Alogliptin benzoate is a white to off-white, crystalline powder containing one asymmetric  
 208 carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble  
 209 in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol  
 210 and isopropyl acetate.

211 Each NESINA tablet contains 34 mg, 17 mg, or 8.5 mg alogliptin benzoate which is  
 212 equivalent to 25 mg, 12.5 mg, or 6.25 mg, respectively, of alogliptin and the following  
 213 inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose,  
 214 croscarmellose sodium, and magnesium stearate. In addition, the film-coating contains  
 215 the following inactive ingredients: hypromellose, titanium dioxide, ferric oxide (red or  
 216 yellow), and polyethylene glycol, and is marked with printing ink (Gray F1).

## 217 12 CLINICAL PHARMACOLOGY

### 218 12.1 Mechanism of Action

219 Increased concentrations of the incretin hormones such as glucagon-like peptide-1  
 220 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the  
 221 bloodstream from the small intestine in response to meals. These hormones cause  
 222 insulin release from the pancreatic beta cells in a glucose-dependent manner but are  
 223 inactivated by the DPP-4 enzyme within minutes. GLP-1 also lowers glucagon secretion  
 224 from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2  
 225 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is  
 226 preserved. Alogliptin is a DPP-4 inhibitor that slows the inactivation of the incretin  
 227 hormones, thereby increasing their bloodstream concentrations and reducing fasting  
 228 and postprandial glucose concentrations in a glucose-dependent manner in patients

229 with type 2 diabetes mellitus. Alogliptin selectively binds to and inhibits DPP-4 but not  
230 DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

## 231 **12.2 Pharmacodynamics**

232 Single-dose administration of NESINA to healthy subjects resulted in a peak inhibition of  
233 DPP-4 within 2 to 3 hours after dosing. The peak inhibition of DPP-4 exceeded 93%  
234 across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24  
235 hours for doses greater than or equal to 25 mg. Peak and total exposure over 24 hours  
236 to active GLP-1 were 3- to 4-fold greater with NESINA (at doses of 25 to 200 mg) than  
237 placebo. In a 16-week, double-blind, placebo-controlled study, NESINA 25 mg  
238 demonstrated decreases in postprandial glucagon while increasing postprandial active  
239 GLP-1 levels compared to placebo over an 8-hour period following a standardized  
240 meal. It is unclear how these findings relate to changes in overall glycemic control in  
241 patients with type 2 diabetes mellitus. In this study, NESINA 25 mg demonstrated  
242 decreases in 2-hour postprandial glucose compared to placebo (-30 mg/dL versus 17  
243 mg/dL, respectively).

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

## 249 **Cardiac Electrophysiology**

250 In a randomized, placebo-controlled, 4-arm, parallel-group study, 257 subjects were  
251 administered either alogliptin 50 mg, alogliptin 400 mg, moxifloxacin 400 mg, or placebo  
252 once-daily for a total of 7 days. No increase in QTc was observed with either dose of  
253 alogliptin. At the 400 mg dose, peak alogliptin plasma concentrations were 19-fold  
254 higher than the peak concentrations following the maximum recommended clinical dose  
255 of 25 mg.

## 256 **12.3 Pharmacokinetics**

257 The pharmacokinetics of NESINA has been studied in healthy subjects and in patients  
258 with type 2 diabetes. After administration of single, oral doses up to 800 mg in healthy  
259 subjects, the peak plasma alogliptin concentration (median  $T_{max}$ ) occurred 1 to 2 hours  
260 after dosing. At the maximum recommended clinical dose of 25 mg, NESINA was  
261 eliminated with a mean terminal half-life ( $T_{1/2}$ ) of approximately 21 hours.

262 After multiple-dose administration up to 400 mg for 14 days in patients with type 2  
263 diabetes, accumulation of alogliptin was minimal with an increase in total (i.e., AUC) and  
264 peak (i.e.,  $C_{max}$ ) alogliptin exposures of 34% and 9%, respectively. Total and peak  
265 exposure to alogliptin increased proportionally across single doses and multiple doses  
266 of alogliptin ranging from 25 mg to 400 mg. The inter-subject coefficient of variation for  
267 alogliptin AUC was 17%. The pharmacokinetics of NESINA was also shown to be  
268 similar in healthy subjects and in patients with type 2 diabetes.

## 269 **Absorption**

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

273 **Distribution**

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

277 Alogliptin is 20% bound to plasma proteins.

278 **Metabolism**

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

281 Two minor metabolites were detected following administration of an oral dose of  
282 [<sup>14</sup>C] alogliptin, *N*-demethylated, M-I (<1% of the parent compound), and *N*-acetylated  
283 alogliptin, M-II (<6% of the parent compound). M-I is an active metabolite and is an  
284 inhibitor of DPP-4 similar to the parent molecule; M-II does not display any inhibitory  
285 activity towards DPP-4 or other DPP-related enzymes. *In vitro* data indicate that  
286 CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

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

290 **Excretion**

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

295 **Specific Populations**

296 **Renal Impairment**

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

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

304 In patients with moderate renal impairment (CrCl ≥30 to <60 mL/min), an approximate  
305 2-fold increase in plasma AUC of alogliptin was observed. To maintain similar systemic  
306 exposures of NESINA to those with normal renal function, the recommended dose is  
307 12.5 mg once daily in patients with moderate renal impairment.

308 In patients with severe renal impairment (CrCl ≥15 to <30 mL/min) and end-stage renal  
309 disease (CrCl <15 mL/min or requiring dialysis), an approximate 3- and 4-fold increase  
310 in plasma AUC of alogliptin were observed, respectively. Dialysis removed  
311 approximately 7% of the drug during a 3-hour dialysis session. NESINA may be  
312 administered without regard to the timing of the dialysis. To maintain similar systemic  
313 exposures of NESINA to those with normal renal function, the recommended dose is

314 6.25 mg once daily in patients with severe renal impairment, as well as in patients with  
315 end-stage renal disease requiring dialysis.

### 316 **Hepatic Impairment**

317 Total exposure to alogliptin was approximately 10% lower and peak exposure was  
318 approximately 8% lower in patients with moderate hepatic impairment (Child-Pugh  
319 Grade B) compared to healthy subjects. The magnitude of these reductions is not  
320 considered to be clinically meaningful. Patients with severe hepatic impairment (Child-  
321 Pugh Grade C) have not been studied. Use caution when administering NESINA to  
322 patients with liver disease [see *Use in Specific Populations (8.6) and Warnings and*  
323 *Precautions (5.3)*].

### 324 **Gender**

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

### 327 **Geriatric**

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

### 330 **Pediatric**

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

### 333 **Race**

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

## 337 **Drug Interactions**

### 338 ***In Vitro Assessment of Drug Interactions***

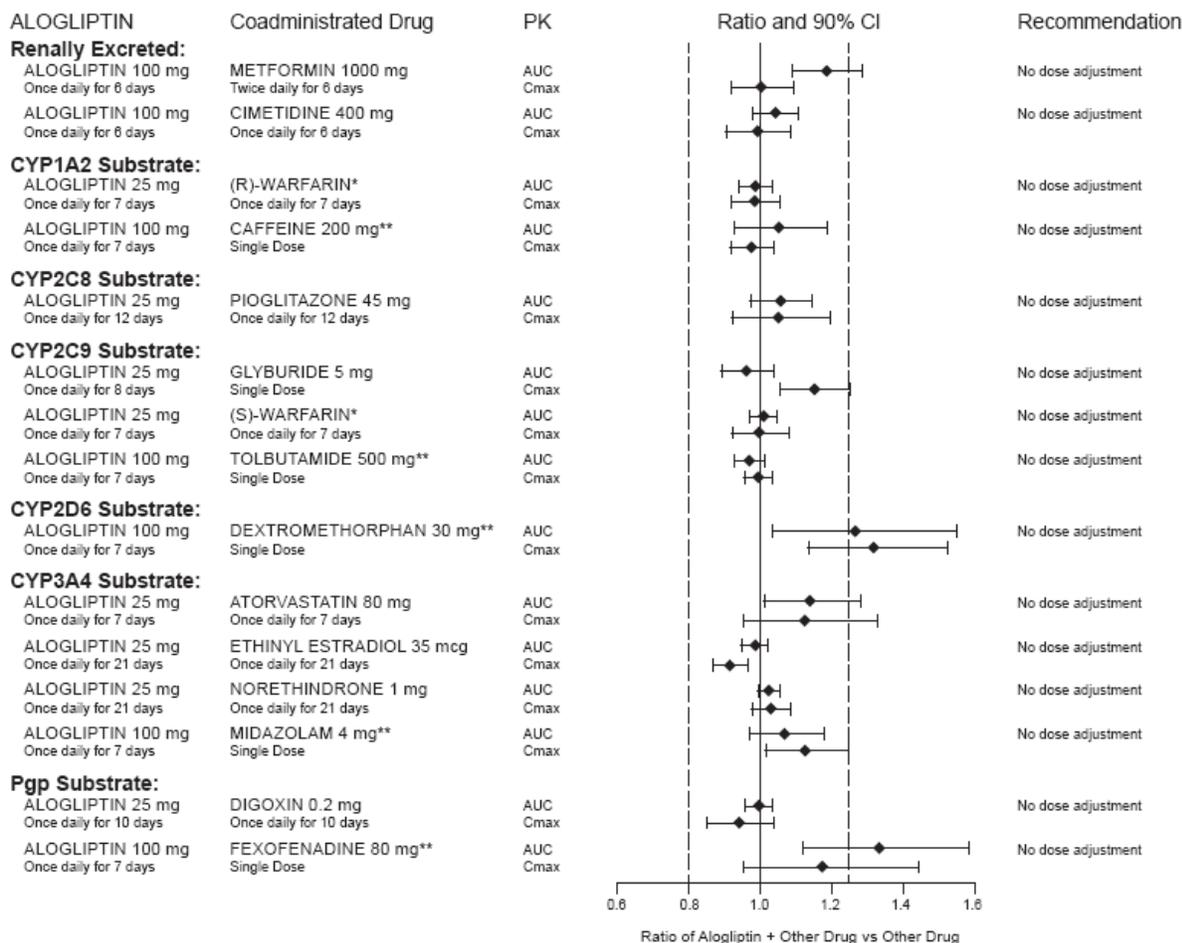
339 *In vitro* studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6,  
340 CYP2C9, CYP2C19, and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9,  
341 CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

### 342 ***In Vivo Assessment of Drug Interactions***

#### 343 **Effects of Alogliptin on the Pharmacokinetics of Other Drugs**

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

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



349

350 \*warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on

351 the prothrombin time (PT) or International Normalized Ratio (INR).

352 \*\*caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam (3A4

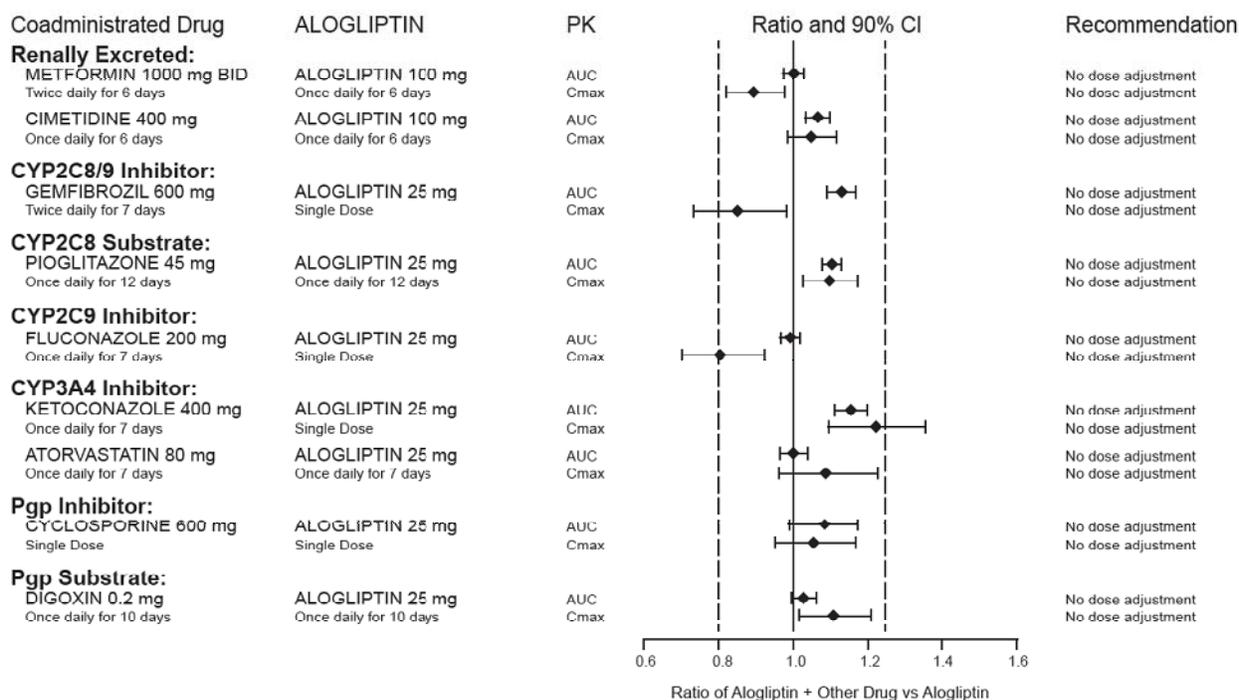
353 substrate), and fexofenadine (P-gp substrate) were administered as a cocktail.

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

355 There are no clinically meaningful changes in the pharmacokinetics of alogliptin when

356 NESINA is administered concomitantly with the drugs described below (*Figure 2*).

357

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

359

360

361 **13 NONCLINICAL TOXICOLOGY**362 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

363 Rats were administered oral doses of 75, 400, and 800 mg/kg alogliptin for 2 years. No  
 364 drug-related tumors were observed up to 75 mg/kg or approximately 32 times the  
 365 maximum recommended clinical dose of 25 mg, based on AUC exposure. At higher  
 366 doses (approximately 308 times the maximum recommended clinical dose of 25 mg), a  
 367 combination of thyroid C-cell adenomas and carcinomas increased in male but not  
 368 female rats. No drug-related tumors were observed in mice after administration of 50,  
 369 150, or 300 mg/kg alogliptin for 2 years, or up to approximately 51-times the maximum  
 370 recommended clinical dose of 25 mg, based on AUC exposure.

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

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

377 **14 CLINICAL STUDIES**

378 NESINA has been studied as monotherapy and in combination with metformin, a  
 379 sulfonylurea, a thiazolidinedione (either alone or in combination with metformin or a  
 380 sulfonylurea), and insulin (either alone or in combination with metformin).

381 A total of 8673 patients with type 2 diabetes were randomized in 10 double-blind,  
382 placebo- or active-controlled clinical safety and efficacy studies conducted to evaluate  
383 the effects of NESINA on glycemic control. The racial distribution of patients exposed to  
384 study medication was 68% Caucasian, 15% Asian, 7% Black, and 9% other racial  
385 groups. The ethnic distribution was 30% Hispanic. Patients had an overall mean age of  
386 55 years (range 21 to 80 years).

387 In patients with type 2 diabetes, treatment with NESINA produced clinically meaningful  
388 and statistically significant improvements in A1C compared to placebo. As is typical for  
389 trials of agents to treat type 2 diabetes, the mean reduction in A1C with NESINA  
390 appears to be related to the degree of A1C elevation at baseline.

391 NESINA had similar changes from baseline in serum lipids compared to placebo.

#### 392 **14.1 Patients with Inadequate Glycemic Control on Diet and Exercise**

393 A total of 1768 patients with type 2 diabetes participated in three double-blind studies to  
394 evaluate the efficacy and safety of NESINA in patients with inadequate glycemic control  
395 on diet and exercise. All three studies had a 4-week, single-blind, placebo run-in period  
396 followed by a 26-week randomized treatment period. Patients who failed to meet pre-  
397 specified hyperglycemic goals during the 26-week treatment periods received glycemic  
398 rescue therapy.

399 In a 26-week, double-blind, placebo-controlled study, a total of 329 patients (mean  
400 baseline A1C = 8%) were randomized to receive NESINA 12.5 mg, NESINA 25 mg, or  
401 placebo once daily. Treatment with NESINA 25 mg resulted in statistically significant  
402 improvements from baseline in A1C and fasting plasma glucose (FPG) compared to  
403 placebo at Week 26 (*Table 3*). A total of 8% of patients receiving NESINA 25 mg and  
404 30% of those receiving placebo required glycemic rescue therapy.

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

406 The mean change in body weight with NESINA was similar to placebo.

<b>Table 3. Glycemic Parameters at Week 26 in a Placebo-Controlled Monotherapy Study of NESINA*</b>		
	<b>NESINA 25 mg</b>	<b>Placebo</b>
<b>A1C (%)</b>	N=128	N=63
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean <sup>†</sup> )	-0.6	0
Difference from placebo (adjusted mean <sup>†</sup> with 95% confidence interval)	-0.6 <sup>‡</sup> (-0.8, -0.3)	—
% of patients (n/N) achieving A1C ≤7%	44% (58/131) <sup>‡</sup>	23% (15/64)
<b>Fasting Plasma Glucose (mg/dL)</b>	N=129	N=64
Baseline (mean)	172	173
Change from baseline (adjusted mean <sup>†</sup> )	-16	11
Difference from placebo (adjusted mean <sup>†</sup> with 95% confidence interval)	-28 <sup>‡</sup> (-40, -15)	—

\*Intent-to-treat population using last observation on study.

<sup>†</sup>Least squares means adjusted for treatment, baseline value, geographic region, and duration of diabetes.

<sup>‡</sup>p<0.01 compared to placebo.

407 In a 26-week, double-blind, active-controlled study, a total of 655 patients (mean  
408 baseline A1C = 8.8%) were randomized to receive NESINA 25 mg alone, pioglitazone  
409 30 mg alone, NESINA 12.5 mg with pioglitazone 30 mg, or NESINA 25 mg with  
410 pioglitazone 30 mg once daily. Coadministration of NESINA 25 mg with pioglitazone 30  
411 mg resulted in statistically significant improvements from baseline in A1C and FPG  
412 compared to NESINA 25 mg alone and to pioglitazone 30 mg alone (*Table 4*). A total of  
413 3% of patients receiving NESINA 25 mg coadministered with pioglitazone 30 mg, 11%  
414 of those receiving NESINA 25 mg alone, and 6% of those receiving pioglitazone 30 mg  
415 alone required glycemic rescue.

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

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

<b>Table 4. Glycemic Parameters at Week 26 in an Active-Controlled Study of NESINA, Pioglitazone, and NESINA in Combination with Pioglitazone*</b>			
	<b>NESINA 25 mg</b>	<b>Pioglitazone 30 mg</b>	<b>NESINA 25 mg + Pioglitazone 30 mg</b>
<b>A1C (%)</b>	N=160	N=153	N=158
Baseline (mean)	8.8	8.8	8.8
Change from baseline (adjusted mean <sup>†</sup> )	-1.0	-1.2	-1.7
Difference from NESINA 25 mg (adjusted mean <sup>†</sup> with 95% confidence interval)	—	—	-0.8 <sup>‡</sup> (-1.0, -0.5)
Difference from pioglitazone 30 mg (adjusted mean <sup>†</sup> with 95% confidence interval)	—	—	-0.6 <sup>‡</sup> (-0.8, -0.3)
% of patients (n/N) achieving A1C ≤7%	24% (40/164)	34% (55/163)	63% (103/164) <sup>‡</sup>
<b>Fasting Plasma Glucose (mg/dL)</b>	N=162	N=157	N=162
Baseline (mean)	189	189	185
Change from baseline (adjusted mean <sup>†</sup> )	-26	-37	-50
Difference from NESINA 25 mg (adjusted mean <sup>†</sup> with 95% confidence interval)	—	—	-24 <sup>‡</sup> (-34, -15)
Difference from pioglitazone 30 mg (adjusted mean <sup>†</sup> with 95% confidence interval)	—	—	-13 <sup>‡</sup> (-22, -4)

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

<sup>†</sup>Least squares means adjusted for treatment, geographic region, and baseline value.

<sup>‡</sup>p<0.01 compared to NESINA 25 mg or pioglitazone 30 mg.

420 In a 26-week, double-blind, placebo-controlled study, a total of 784 patients  
421 inadequately controlled on diet and exercise alone (mean baseline A1C = 8.4%) were  
422 randomized to 1 of 7 treatment groups: placebo; metformin HCl 500 mg or metformin  
423 HCl 1000 mg twice daily, NESINA 12.5 mg twice daily, or NESINA 25 mg daily; NESINA  
424 12.5 mg in combination with metformin HCl 500 mg or metformin HCl 1000 mg twice  
425 daily. Both coadministration treatment arms (NESINA 12.5 mg + metformin HCl 500 mg  
426 and NESINA 12.5 mg + metformin HCl 1000 mg) resulted in statistically significant  
427 improvements in A1C and FPG when compared with their respective individual  
428 alogliptin and metformin component regimens (*Table 5*). Coadministration treatment  
429 arms demonstrated improvements in 2-hour postprandial glucose (PPG) compared to  
430 NESINA alone or metformin alone (*Table 5*). A total of 12.3% of patients receiving  
431 NESINA 12.5 mg + metformin HCl 500 mg, 2.6% of patients receiving NESINA 12.5 mg  
432 + metformin HCl 1000 mg, 17.3% of patients receiving NESINA 12.5 mg, 22.9% of  
433 patients receiving metformin HCl 500 mg, 10.8% of patients receiving metformin HCl  
434 1000 mg and 38.7% of patients receiving placebo required glycemic rescue.

435 Improvements in A1C were not affected by gender, age, race, or baseline BMI. The  
436 mean decrease in body weight was similar between metformin alone and NESINA when  
437 coadministered with metformin.  
438

<b>Table 5. Glycemic Parameters at Week 26 for NESINA and Metformin Alone and in Combination in Patients with Type 2 Diabetes</b>						
	Placebo	NESINA 12.5 mg twice daily	Metformin HCl 500 mg twice daily	Metformin HCl 1000 mg twice daily	NESINA 12.5 mg + Metformin HCl 500 mg twice daily	NESINA 12.5 mg + Metformin HCl 1000 mg twice daily
<b>A1C (%)*</b>	N=102	N=104	N=103	N=108	N=102	N=111
Baseline (mean)	8.5	8.4	8.5	8.4	8.5	8.4
Change from baseline (adjusted mean <sup>†</sup> )	0.1	-0.6	-0.7	-1.1	-1.2	-1.6
Difference from metformin (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-0.6 <sup>‡</sup> (-0.9, -0.3)	-0.4 <sup>‡</sup> (-0.7, -0.2)
Difference from NESINA (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-0.7 <sup>‡</sup> (-1.0, -0.4)	-1.0 <sup>‡</sup> (-1.3, -0.7)
% Patients (n/N) achieving A1C <7% <sup>§</sup>	4% (4/102)	20% (21/104)	27% (28/103)	34% (37/108)	47% <sup>‡</sup> (48/102)	59% <sup>‡</sup> (66/111)
<b>FPG (mg/dL)*</b>	N=105	N=106	N=106	N=110	N=106	N=112
Baseline (mean)	187	177	180	181	176	185
Change from baseline (adjusted mean <sup>†</sup> )	12	-10	-12	-32	-32	-46
Difference from metformin (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-20 <sup>‡</sup> (-33, -8)	-14 <sup>‡</sup> (-26, -2)
Difference from NESINA (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-22 <sup>‡</sup> (-35, -10)	-36 <sup>‡</sup> (-49, -24)
<b>2-Hour PPG (mg/dL)<sup>¶</sup></b>	N=26	N=34	N=28	N=37	N=31	N=37
Baseline (mean)	263	272	247	266	261	268
Change from baseline (adjusted mean <sup>†</sup> )	-21	-43	-49	-54	-68	-86 <sup>‡</sup>
Difference from metformin (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-19 (-49, 11)	-32 <sup>‡</sup> (-58, -5)
Difference from NESINA (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-25 (-53, -3)	-43 <sup>‡</sup> (-70, -16)

\*Intent-to-treat population using last observation on study prior to discontinuation of double-blind study medication or sulfonylurea rescue therapy for patients needing rescue.

<sup>†</sup>Least squares means adjusted for treatment, geographic region and baseline value.

<sup>‡</sup> p<0.05 when compared to metformin and NESINA alone.

<sup>§</sup>Compared using logistic regression.

<sup>¶</sup> Intent-to-treat population using data available at Week 26.

441 **14.2 Combination Therapy**

442 ***Add-On Therapy to Metformin***

443 A total of 2081 patients with type 2 diabetes participated in two 26-week double-blind,  
444 placebo-controlled studies to evaluate the efficacy and safety of NESINA as add-on  
445 therapy to metformin. In both studies, patients were inadequately controlled on  
446 metformin at a dose of at least 1500 mg per day or at the maximum tolerated dose. All  
447 patients entered a 4-week, single-blind, placebo run-in period prior to randomization.  
448 Patients who failed to meet pre-specified hyperglycemic goals during the 26-week  
449 treatment periods received glycemic rescue therapy.

450 In the first 26-week, placebo-controlled study, a total of 527 patients already on  
451 metformin (mean baseline A1C = 8%) were randomized to receive NESINA 12.5 mg,  
452 NESINA 25 mg, or placebo. Patients were maintained on a stable dose of metformin  
453 (median dose = 1700 mg) during the treatment period. NESINA 25 mg in combination  
454 with metformin resulted in statistically significant improvements from baseline in A1C  
455 and FPG at Week 26, when compared to placebo (*Table 6*). A total of 8% of patients  
456 receiving NESINA 25 mg and 24% of patients receiving placebo required glycemic  
457 rescue.

458 Improvements in A1C were not affected by gender, age, baseline BMI, or baseline  
459 metformin dose.

460 The mean decrease in body weight was similar between NESINA and placebo when  
461 given in combination with metformin.

462

<b>Table 6. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of NESINA as Add-on Therapy to Metformin*</b>		
	<b>NESINA 25 mg + Metformin</b>	<b>Placebo + Metformin</b>
<b>A1C (%)</b>	N=203	N=103
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean <sup>†</sup> )	-0.6	-0.1
Difference from placebo (adjusted mean <sup>†</sup> with 95% confidence interval)	-0.5 <sup>‡</sup> (-0.7, -0.3)	—
% of patients (n/N) achieving A1C ≤7%	44% (92/207) <sup>‡</sup>	18% (19/104)
<b>Fasting Plasma Glucose (mg/dL)</b>	N=204	N=104
Baseline (mean)	172	180
Change from baseline (adjusted mean <sup>†</sup> )	-17	0
Difference from placebo (adjusted mean <sup>†</sup> with 95% confidence interval)	-17 <sup>‡</sup> (-26, -9)	—

\*Intent-to-treat population using last observation on study.

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

<sup>‡</sup>p<0.001 compared to placebo.

463 In the second 26-week double-blind, placebo-controlled study, a total of 1554 patients  
 464 already on metformin (mean baseline A1C = 8.5%) were randomized to one of 12  
 465 double-blind treatment groups: placebo; 12.5 mg or 25 mg of NESINA alone; 15 mg, 30  
 466 mg, or 45 mg of pioglitazone alone; or 12.5 mg or 25 mg of NESINA in combination with  
 467 15 mg, 30 mg, or 45 mg of pioglitazone. Patients were maintained on a stable dose of  
 468 metformin (median dose = 1700 mg) during the treatment period. Coadministration of  
 469 NESINA and pioglitazone provided statistically significant improvements in A1C and  
 470 FPG compared to placebo, to NESINA alone, or to pioglitazone alone when added to  
 471 background metformin therapy (*Table 7, Figure 3*). In addition, improvements from  
 472 baseline A1C were comparable between NESINA alone and pioglitazone alone (15 mg,  
 473 30 mg, and 45 mg) at Week 26. A total of 4%, 5%, or 2% of patients receiving NESINA  
 474 25 mg with 15 mg, 30 mg, or 45 mg pioglitazone, 33% of patients receiving placebo,  
 475 13% of patients receiving NESINA 25 mg, and 10%, 15%, or 9% of patients receiving  
 476 pioglitazone 15 mg, 30 mg, or 45 mg alone required glycemic rescue.

- 477 Improvements in A1C were not affected by gender, age, or baseline BMI.
- 478 The mean increase in body weight was similar between pioglitazone alone and NESINA
- 479 when coadministered with pioglitazone.

	Placebo	NESINA 25 mg	Pioglitazone 15 mg	Pioglitazone 30 mg	Pioglitazone 45 mg	NESINA 25 mg + Pioglitazone 15 mg	NESINA 25 mg + Pioglitazone 30 mg	NESINA 25 mg + Pioglitazone 45 mg
<b>A1C (%)</b>	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 <sup>†</sup> )	-0.1	-0.9	-0.8	-0.9	-1.0	-1.3 <sup>‡</sup>	-1.4 <sup>‡</sup>	-1.6 <sup>‡</sup>
Difference from pioglitazone (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-	-0.5 <sup>‡</sup> (-0.7, -0.3)	-0.5 <sup>‡</sup> (-0.7, -0.3)	-0.6 <sup>‡</sup> (-0.8, -0.4)
Difference from NESINA (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-	-0.4 <sup>‡</sup> (-0.6, -0.1)	-0.5 <sup>‡</sup> (-0.7, -0.3)	-0.7 <sup>‡</sup> (-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) <sup>‡</sup>	53% (69/130) <sup>‡</sup>	60% (78/130) <sup>‡</sup>
<b>Fasting Plasma Glucose (mg/dL)</b>	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 <sup>†</sup> )	7	-19	-24	-29	-32	-38 <sup>‡</sup>	-42 <sup>‡</sup>	-53 <sup>‡</sup>
Difference from pioglitazone (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-	-14 <sup>‡</sup> (-24, -5)	-13 <sup>‡</sup> (-23, -3)	-20 <sup>‡</sup> (-30, -11)
Difference from NESINA (adjusted mean <sup>†</sup> with 95% confidence interval)	-	-	-	-	-	-19 <sup>‡</sup> (-29, -10)	-23 <sup>‡</sup> (-33, -13)	-34 <sup>‡</sup> (-44, -24)

\*Intent-to-treat population using last observation on study.

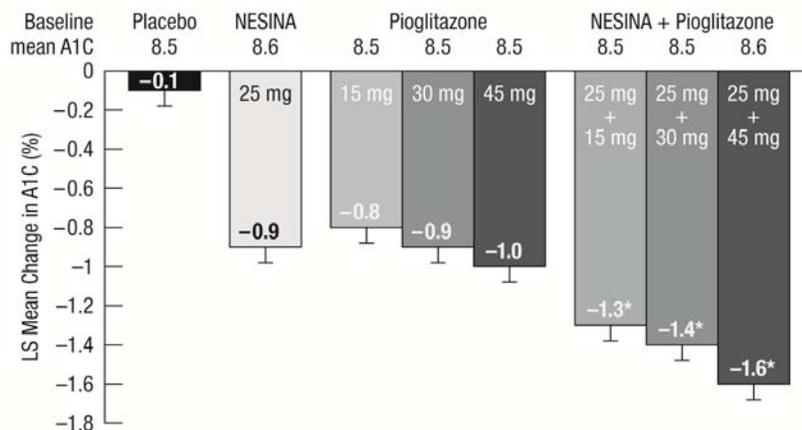
<sup>†</sup>Least squares means adjusted for treatment, geographic region, metformin dose and baseline value.

<sup>‡</sup>p≤0.01 when compared to corresponding doses of pioglitazone and NESINA alone.

480

481  
482  
483  
484  
485

**Figure 3. Change From Baseline in A1C at Week 26 with NESINA and Pioglitazone Alone and NESINA in Combination with Pioglitazone When Added to Metformin**



Intent-to-treat population using last observation on study.  
\* $P \leq 0.001$  compared to corresponding doses of NESINA alone or Pioglitazone alone.

486

#### 487 **Add-On Therapy to a Thiazolidinedione**

488 In a 26-week, placebo-controlled study, a total of 493 patients inadequately controlled  
489 on a thiazolidinedione alone or in combination with metformin or a sulfonylurea (10 mg)  
490 (mean baseline A1C = 8%) were randomized to receive NESINA 12.5 mg, NESINA 25  
491 mg, or placebo. Patients were maintained on a stable dose of pioglitazone (median  
492 dose = 30 mg) during the treatment period; those who were also previously treated on  
493 metformin (median dose = 2000 mg) or sulfonylurea (median dose = 10 mg) prior to  
494 randomization were maintained on the combination therapy during the treatment period.  
495 All patients entered into a 4-week single-blind, placebo run-in period prior to  
496 randomization. Patients who failed to meet pre-specified hyperglycemic goals during the  
497 26-week treatment period received glycemic rescue therapy.

498 The addition of NESINA 25 mg once daily to pioglitazone therapy resulted in statistically  
499 significant improvements from baseline in A1C and FPG at Week 26, compared to  
500 placebo (Table 8). A total of 9% of patients who were receiving NESINA 25 mg and  
501 12% of patients receiving placebo required glycemic rescue.

502 Improvements in A1C were not affected by gender, age, baseline BMI, or baseline  
503 pioglitazone dose.

504 Clinically meaningful reductions in A1C were observed with NESINA compared to  
505 placebo regardless of whether subjects were receiving concomitant metformin or  
506 sulfonylurea (-0.2% placebo versus -0.9% NESINA) therapy or pioglitazone alone (0%  
507 placebo versus -0.52% NESINA).

508 The mean increase in body weight was similar between NESINA and placebo when  
509 given in combination with pioglitazone.

<b>Table 8. Glycemic Parameters in a 26-Week, Placebo-Controlled Study of NESINA as Add-on Therapy to Pioglitazone*</b>		
	<b>NESINA 25 mg + Pioglitazone ± Metformin ± Sulfonylurea</b>	<b>Placebo + Pioglitazone ± Metformin ± Sulfonylurea</b>
<b>A1C (%)</b>	N=195	N=95
Baseline (mean)	8	8
Change from baseline (adjusted mean <sup>†</sup> )	-0.8	-0.2
Difference from placebo (adjusted mean <sup>†</sup> with 95%confidence interval)	-0.6 <sup>‡</sup> (-0.8, -0.4)	—
% of patients (n/N) achieving A1C ≤7%	49% (98/199) <sup>‡</sup>	34% (33/97)
<b>Fasting Plasma Glucose (mg/dL)</b>	N=197	N=97
Baseline (mean)	170	172
Change from baseline (adjusted mean <sup>†</sup> )	-20	-6
Difference from placebo (adjusted mean <sup>†</sup> with 95%confidence interval)	-14 <sup>‡</sup> (-23, -5)	—

\*Intent-to-treat population using last observation on study.

†Least squares means adjusted for treatment, baseline value, geographic region, baseline treatment regimen (pioglitazone, pioglitazone + metformin, or pioglitazone + sulfonylurea), and baseline pioglitazone dose.

‡p<0.01 compared to placebo.

### 510 **Add-on Combination Therapy with Pioglitazone and Metformin**

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

519 In combination with pioglitazone and metformin, NESINA 25 mg was shown to be  
520 statistically superior in lowering A1C and FPG compared with the titration of  
521 pioglitazone from 30 mg to 45 mg at Week 26 and at Week 52 (*Table 9; results shown*  
522 *only for Week 52*). A total of 11% of patients in the NESINA 25 mg treatment group and  
523 22% of patients in the pioglitazone up titration group required glycemic rescue.

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

525 The mean increase in body weight was similar in both treatment arms.

<b>Table 9. Glycemic Parameters in a 52-Week, Controlled Study of NESINA as Add-On Combination Therapy With Pioglitazone and Metformin*</b>		
	<b>NESINA 25 mg + Pioglitazone 30 mg + Metformin</b>	<b>Pioglitazone 45 mg + Metformin</b>
<b>A1C (%)</b>	N=397	N=394
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean <sup>†</sup> )	-0.7	-0.3
Difference from pioglitazone 45 mg + metformin (adjusted mean <sup>†</sup> with 95% confidence interval)	-0.4 <sup>‡</sup> (-0.5, -0.3)	—
% of patients (n/N) achieving A1C<7%	33% (134/404) <sup>§</sup>	21% (85/399)
<b>Fasting Plasma Glucose (mg/dL)</b>	N=399	N=396
Baseline (mean)	162	162
Change from baseline (adjusted mean <sup>†</sup> )	-15	-4
Difference from pioglitazone 45 mg + metformin (adjusted mean <sup>†</sup> with 95% confidence interval)	-11 <sup>§</sup> (-16, -6)	—

\*Intent-to-treat population using last observation on study.

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

<sup>‡</sup> Non-inferior and statistically superior to metformin + pioglitazone at the 0.025 one-sided significance level.

<sup>§</sup> p<0.001 compared to pioglitazone 45 mg + metformin

### 526 **Add-On Therapy to a Sulfonylurea**

527 In a 26-week, placebo-controlled study, a total of 500 patients inadequately controlled  
528 on a sulfonylurea (mean baseline A1C = 8.1%) were randomized to receive NESINA  
529 12.5 mg, NESINA 25 mg, or placebo. Patients were maintained on a stable dose of  
530 glyburide (median dose = 10 mg) during the treatment period. All patients entered into a  
531 4-week single-blind, placebo run-in period prior to randomization. Patients who failed to  
532 meet pre-specified hyperglycemic goals during the 26-week treatment period received  
533 glycemic rescue therapy.

534 The addition of NESINA 25 mg to glyburide therapy resulted in statistically significant  
535 improvements from baseline in A1C at Week 26 when compared to placebo (*Table 10*).  
536 Improvements in FPG observed with NESINA 25 mg were not statistically significant  
537 compared with placebo. A total of 16% of patients receiving NESINA 25 mg and 28% of  
538 those receiving placebo required glycemic rescue.

539 Improvements in A1C were not affected by gender, age, baseline BMI, or baseline  
540 glyburide dose.

541 The mean change in body weight was similar between NESINA and placebo when  
 542 given in combination with glyburide.

543

<b>Table 10. Glycemic Parameters in a 26-Week, Placebo-Controlled Study of NESINA as Add-on Therapy to Glyburide*</b>		
	<b>NESINA 25 mg + Glyburide</b>	<b>Placebo + Glyburide</b>
<b>A1C (%)</b>	N=197	N=97
Baseline (mean)	8.1	8.2
Change from baseline (adjusted mean <sup>†</sup> )	-0.5	0
Difference from placebo (adjusted mean <sup>†</sup> with 95% confidence interval)	-0.5 <sup>‡</sup> (-0.7, -0.3)	—
% of patients (n/N) achieving A1C ≤7%	35% (69/198) <sup>‡</sup>	18% (18/99)
<b>Fasting Plasma Glucose (mg/dL)</b>	N=198	N=99
Baseline (mean)	174	177
Change from baseline (adjusted mean <sup>†</sup> )	-8	2
Difference from placebo (adjusted mean <sup>†</sup> with 95% confidence interval)	-11 (-22, 1)	—

\*Intent-to-treat population using last observation on study.

<sup>†</sup>Least squares means adjusted for treatment, baseline value, geographic region, and baseline glyburide dose.

<sup>‡</sup>p<0.01 compared to placebo.

#### 544 **Add-On Therapy to Insulin**

545 In a 26-week, placebo-controlled study, a total of 390 patients inadequately controlled  
 546 on insulin alone (42%) or in combination with metformin (58%) (mean baseline A1C =  
 547 9.3%) were randomized to receive NESINA 12.5 mg, NESINA 25 mg, or placebo.  
 548 Patients were maintained on their insulin regimen (median dose = 55 IU) upon  
 549 randomization and those previously treated with insulin in combination with metformin  
 550 (median dose = 1700 mg) prior to randomization continued on the combination regimen  
 551 during the treatment period. Patients entered the trial on short-, intermediate- or long-  
 552 acting (basal) insulin or premixed insulin. Patients who failed to meet pre-specified  
 553 hyperglycemic goals during the 26 month treatment period received glycemic rescue  
 554 therapy.

555 The addition of NESINA 25 mg once daily to insulin therapy resulted in statistically  
 556 significant improvements from baseline in A1C and FPG at Week 26, when compared to  
 557 placebo (*Table 11*). A total of 20% of patients receiving NESINA 25 mg and 40% of  
 558 those receiving placebo required glycemic rescue.

559 Improvements in A1C were not affected by gender, age, baseline BMI, or baseline  
 560 insulin dose. Clinically meaningful reductions in A1C were observed with NESINA  
 561 compared to placebo regardless of whether subjects were receiving concomitant  
 562 metformin and insulin (-0.2% placebo versus -0.8% NESINA) therapy or insulin alone  
 563 (0.1% placebo versus -0.7% NESINA).

564 The mean increase in body weight was similar between NESINA and placebo when  
 565 given in combination with insulin.

<b>Table 11. Glycemic Parameters in a 26-Week, Placebo-Controlled Study of NESINA as Add-on Therapy to Insulin*</b>		
	<b>NESINA 25 mg + Insulin ± Metformin</b>	<b>Placebo + Insulin ± Metformin</b>
<b>A1C (%)</b>	N=126	N=126
Baseline (mean)	9.3	9.3
Change from baseline (adjusted mean <sup>†</sup> )	-0.7	-0.1
Difference from placebo (adjusted mean <sup>†</sup> with 95% confidence interval)	-0.6 <sup>‡</sup> (-0.8, -0.4)	—
% of patients (n/N) achieving A1C ≤7%	8% (10/129)	1% (1/129)
<b>Fasting Plasma Glucose (mg/dL)</b>	N=128	N=127
Baseline (mean)	186	196
Change from baseline (adjusted mean <sup>†</sup> )	-12	6
Difference from placebo (adjusted mean <sup>†</sup> with 95% confidence interval)	-18 <sup>‡</sup> (-33, -2)	—

\*Intent-to-treat population using last observation on study.

†Least squares means adjusted for treatment, baseline value, geographic region, baseline treatment regimen (insulin or insulin + metformin), and baseline daily insulin dose.

‡p<0.05 compared to placebo.

## 566 **16 HOW SUPPLIED/STORAGE AND HANDLING**

567 NESINA tablets are available as film-coated tablets containing 25 mg, 12.5 mg or 6.25  
 568 mg of alogliptin as follows:

569 25 mg tablet: light red, oval, biconvex, film-coated, with “TAK ALG-25” printed on one  
 570 side, available in:

NDC 64764-250-30      Bottles of 30 tablets

NDC 64764-250-90      Bottles of 90 tablets  
NDC 64764-250-50      Bottles of 500 tablets

571 12.5 mg tablet: yellow, oval, biconvex, film-coated, with “TAK ALG-12.5” printed on one  
572 side, available in:

NDC 64764-125-30      Bottles of 30 tablets  
NDC 64764-125-90      Bottles of 90 tablets  
NDC 64764-125-50      Bottles of 500 tablets

573 6.25 mg tablet: light pink, oval, biconvex, film-coated, with “TAK ALG-6.25” printed on  
574 one side, available in:

NDC 64764-625-30      Bottles of 30 tablets  
NDC 64764-625-90      Bottles of 90 tablets

## 575 **Storage**

576 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP  
577 Controlled Room Temperature].

## 578 **17 PATIENT COUNSELING INFORMATION**

579 *See FDA-Approved Patient Labeling (Medication Guide)*

### 580 **17.1 Instructions**

581 Inform patients of the potential risks and benefits of NESINA.

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

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

593 Patients should be informed that postmarketing reports of liver injury, sometimes fatal,  
594 have been reported during use of NESINA. If signs or symptoms of liver injury occur,  
595 patients should be instructed to discontinue NESINA and seek medical advice promptly.

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

599 Instruct patients to take NESINA only as prescribed. If a dose is missed, advise patients  
600 not to double their next dose.

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

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606 Deerfield, IL 60015

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612 NES011 R1-V3.4

613

614 **MEDICATION GUIDE**

615

## MEDICATION GUIDE

### NESINA (nes-see'-na) (alogliptin) tablets

Read this Medication Guide carefully before you start taking NESINA 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 treatment. If you have any questions about NESINA, ask your doctor or pharmacist.

#### **What is the most important information I should know about NESINA?**

**Serious side effects can happen to people taking NESINA**, including inflammation of the pancreas (pancreatitis) which may be severe.

Certain medical conditions make you more likely to get pancreatitis.

#### **Before you start taking NESINA:**

Tell your doctor if you have ever had:

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- kidney problems
- liver problems

Stop taking NESINA 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 NESINA?**

- NESINA is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- NESINA is unlikely by itself to cause your blood sugar to be lowered to a dangerous level (hypoglycemia). However, hypoglycemia may still occur with NESINA.
- NESINA is not for people with type 1 diabetes.
- NESINA is not for people with diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if NESINA is safe and effective in children under the age of 18.

## Who should not take NESINA?

### Do not take NESINA if you:

- Are allergic to any ingredients in NESINA or have had a serious allergic (hypersensitivity) reaction to NESINA. See the end of this Medication Guide for a complete list of the ingredients in NESINA.
- Symptoms of a serious allergic reaction to NESINA 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 any of these symptoms, stop taking NESINA 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 NESINA?

Before you take NESINA, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis)
- have kidney or liver problems
- have other medical conditions
- are pregnant or plan to become pregnant. It is not known if NESINA can harm your unborn baby. Talk with your doctor about the best way to control your blood sugar while you are pregnant or if you plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known whether NESINA passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking NESINA.

**Tell your doctor about all the medicines you take**, including prescription and nonprescription 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 any new medicine.

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

## How should I take NESINA?

- Take NESINA exactly as your doctor tells you to take it.
- Take NESINA 1 time each day with or without food.
- 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 NESINA at the same time.

- If you take too much NESINA, 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 NESINA and during treatment as needed. Your doctor may change your dose of NESINA 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.

### What are the possible side effects of NESINA?

#### NESINA can cause serious side effects, including:

See “What is the most important information I should know about NESINA?”

- **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 NESINA 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
- **Low blood sugar (hypoglycemia).** If you take NESINA 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 NESINA. 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 include:
  - shaking or feeling jittery
  - fast heartbeat
  - sweating
  - change in vision

- hunger
- headache
- change in mood
- confusion
- dizziness

The most common side effects of NESINA include:

- stuffy or runny nose and sore throat
- headache
- 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 NESINA. 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 NESINA?**

Store NESINA at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep NESINA and all medicines out of the reach of children.**

### **General information about the safe and effective use of NESINA**

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not take NESINA for a condition for which it was not prescribed. Do not give NESINA 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 NESINA. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about NESINA that is written for health professionals.

For more information go to [www.NESINA.com](http://www.NESINA.com) or call 1-877-TAKEDA-7 (1-877-825-3327).

### **What are the ingredients in NESINA?**

**Active ingredient:** alogliptin

**Inactive ingredients:** mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film-coating contains the following inactive ingredients: hypromellose, titanium dioxide, ferric oxide (red or yellow), and polyethylene glycol, and is marked with gray F1 printing ink.

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

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