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.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

NESINA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings *[see Clinical Studies (14)].*

1.2 Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of NESINA is 25 mg once daily.

NESINA may be taken with or without food.

2.2 Patients with Renal Impairment

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

- 25 mg tablets are light red, oval, biconvex, film-coated, with “TAK ALG-25” printed on one side.
- 12.5 mg tablets are yellow, oval, biconvex, film-coated, with “TAK ALG-12.5” printed on one side.
- 6.25 mg tablets are light pink, oval, biconvex, film-coated, with “TAK ALG-6.25” printed on one side.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

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

5.2 Hypersensitivity Reactions

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

5.3 Hepatic Effects

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

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

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

5.4 Use with Medications Known to Cause Hypoglycemia

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

5.5 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

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

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

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

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

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

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

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Table 1. Adverse Reactions Reported in ≥4% Patients Treated with NESINA 25 mg and More Frequently Than in Patients Given Placebo in Pooled Studies

	Number of Patients (%)		
	NESINA 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)

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

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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

Add-on to Glyburide (26 Weeks)	**NESINA 25 mg + Glyburide**	**Placebo + Glyburide**
	N=198	N=99
Overall (%)	19 (9.6)	11 (11.1)
Severe (%)†	0	1 (1)
Add-on to Insulin (+/- Metformin) (26 Weeks)	**NESINA 25 mg + Insulin (+/- Metformin)**	**Placebo + Insulin (+/- Metformin)**
	N=129	N=129
Overall (%)	35 (27)	31 (24)
Severe (%)†	1 (0.8)	2 (1.6)
Add-on to Metformin (26 Weeks)	**NESINA 25 mg + Metformin**	**Placebo + Metformin**
	N=207	N=104
Overall (%)	0	3 (2.9)
Severe (%)†	0	0
Add-on to Pioglitazone (± Metformin or Sulfonylurea) (26 Weeks)	**NESINA 25 mg + Pioglitazone**	**Placebo + Pioglitazone**
	N=199	N=97
Overall (%)	14 (7.0)	5 (5.2)
Severe (%)†	0	1 (1)
Compared to Glipizide (52 Weeks)	**NESINA 25 mg**	**Glipizide**
	N=222	N=219
Overall (%)	12 (5.4)	57 (26)
Severe (%)†	0	3 (1.4)
Add on to Metformin (26 Weeks)	**NESINA 25 mg**	**Metformin 500 mg twice daily**
	N=112	N=109

Overall (%)	2 (1.8)	2 (1.8)
Severe (%)†	0	0
Add on to Metformin Compared to Glipizide (52 Weeks)	**NESINA 25 mg + Metformin**	**Glipizide + Metformin**
	N=877	N=869
Overall (%)	12 (1.4)	207 (23.8)
Severe (%)†	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.

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

Vital Signs

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

Laboratory Tests

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

6.2 Postmarketing Experience

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

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

10 OVERDOSAGE

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

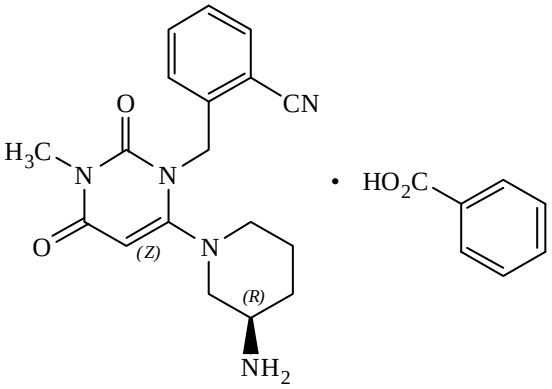
In the event of an overdose, it is reasonable to institute the necessary clinical monitoring and supportive therapy as dictated by the patient's clinical status. Per clinical judgment, it may be reasonable to initiate removal of unabsorbed material from the gastrointestinal tract.

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

11 DESCRIPTION

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

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



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

Each NESINA tablet contains 34 mg, 17 mg, or 8.5 mg alogliptin benzoate which is equivalent to 25 mg, 12.5 mg, or 6.25 mg, respectively, of alogliptin and the following 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 printing ink (Gray F1).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

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

Absorption

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

Distribution

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

Alogliptin is 20% bound to plasma proteins.

Metabolism

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

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

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

Excretion

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

Specific Populations

Renal Impairment

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

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

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

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

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

Hepatic Impairment

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

Gender

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

Geriatric

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

Pediatric

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

Race

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

Drug Interactions

In Vitro Assessment of Drug Interactions

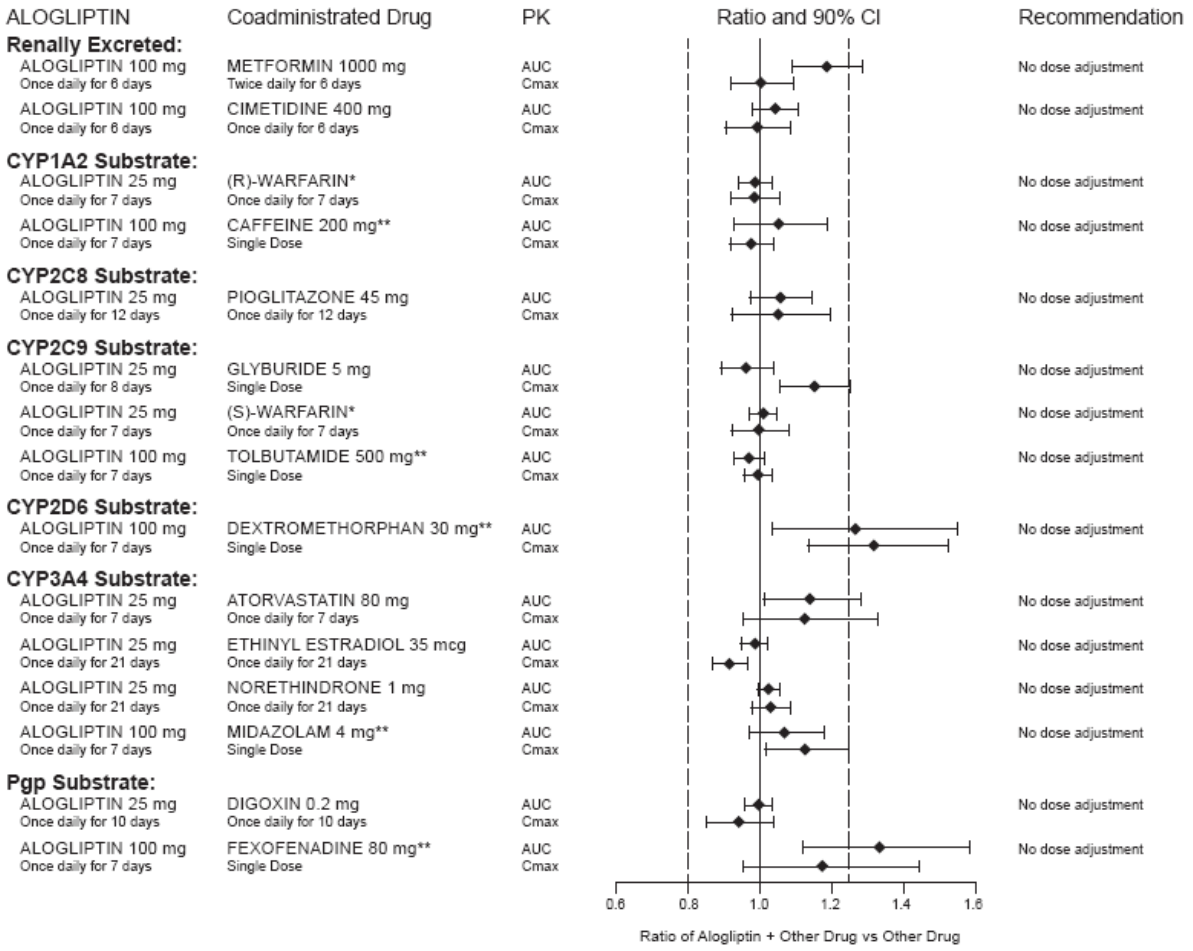
In vitro studies indicate that alogliptin is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4, nor an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP2D6 at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions

Effects of Alogliptin on the Pharmacokinetics of Other Drugs

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

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



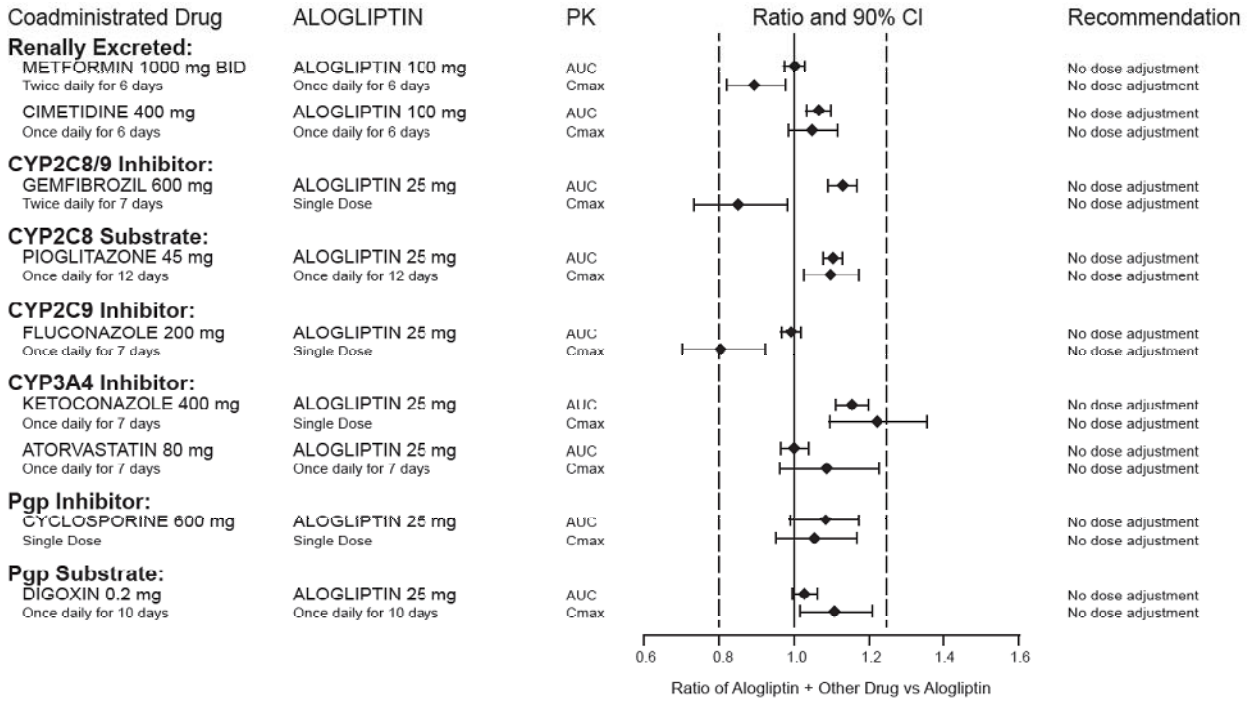
*warfarin was given once daily at a stable dose in the range of 1 mg to 10 mg. Alogliptin had no significant effect on the prothrombin time (PT) or International Normalized Ratio (INR).

**caffeine (1A2 substrate), tolbutamide (2C9 substrate), dextromethorphan (2D6 substrate), midazolam (3A4 substrate), and fexofenadine (P-gp substrate) were administered as a cocktail.

Effects of Other Drugs on the Pharmacokinetics of Alogliptin

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

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



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

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

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

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

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

14.1 Patients with Inadequate Glycemic Control on Diet and Exercise

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

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

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

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

Table 3. Glycemic Parameters at Week 26 in a Placebo-Controlled Monotherapy Study of NESINA*

	NESINA 25 mg	Placebo
A1C (%)	N=128	N=63
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean†)	-0.6	0
Difference from placebo (adjusted mean† with 95% confidence interval)	-0.6‡ (-0.8, -0.3)	—
% of patients (n/N) achieving A1C ≤7%	44% (58/131)‡	23% (15/64)
Fasting Plasma Glucose (mg/dL)	N=129	N=64
Baseline (mean)	172	173
Change from baseline (adjusted mean†)	-16	11
Difference from placebo (adjusted mean† with 95% confidence interval)	-28‡ (-40, -15)	—

*Intent-to-treat population using last observation on study.
†Least squares means adjusted for treatment, baseline value, geographic region, and duration of diabetes.
‡p<0.01 compared to placebo.

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

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

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

Table 4. Glycemic Parameters at Week 26 in an Active-Controlled Study of NESINA, Pioglitazone, and NESINA in Combination with Pioglitazone*

	NESINA 25 mg	Pioglitazone 30 mg	NESINA 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†)	-1.0	-1.2	-1.7
Difference from NESINA 25 mg (adjusted mean† with 95% confidence interval)	—	—	-0.8‡ (-1.0, -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 NESINA 25 mg (adjusted mean† with 95%confidence interval)	—	—	-24‡ (-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 NESINA 25 mg or pioglitazone 30 mg.

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

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

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Table 5. Glycemic Parameters at Week 26 for NESINA and Metformin Alone and in Combination in Patients with Type 2 Diabetes

	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
A1C (%)*	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†)	0.1	-0.6	-0.7	-1.1	-1.2	-1.6
Difference from metformin (adjusted mean† with 95% confidence interval)	-	-	-	-	-0.6‡ (-0.9, -0.3)	-0.4‡ (-0.7, -0.2)
Difference from NESINA (adjusted mean† with 95% confidence interval)	-	-	-	-	-0.7‡ (-1.0, -0.4)	-1.0‡ (-1.3, -0.7)
% Patients (n/N) achieving A1C <7%§	4% (4/102)	20% (21/104)	27% (28/103)	34% (37/108)	47%‡ (48/102)	59%‡ (66/111)
FPG (mg/dL)*	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†)	12	-10	-12	-32	-32	-46
Difference from metformin (adjusted mean† with 95% confidence interval)	-	-	-	-	-20‡ (-33, -8)	-14‡ (-26, -2)
Difference from NESINA (adjusted mean† with 95% confidence interval)	-	-	-	-	-22‡ (-35, -10)	-36‡ (-49, -24)
2-Hour PPG (mg/dL) ¶	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†)	-21	-43	-49	-54	-68	-86‡
Difference from metformin (adjusted mean† with 95% confidence interval)	-	-	-	-	-19 (-49, 11)	-32‡ (-58, -5)
Difference from NESINA (adjusted mean† with 95% confidence interval)	-	-	-	-	-25 (-53, -3)	-43‡ (-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.
†Least squares means adjusted for treatment, geographic region and baseline value.
‡ p<0.05 when compared to metformin and NESINA alone.
§Compared using logistic regression.
¶ Intent-to-treat population using data available at Week 26.

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14.2 Combination Therapy

Add-On Therapy to Metformin

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

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

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

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

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Table 6. Glycemic Parameters at Week 26 in a Placebo-Controlled Study of NESINA as Add-on Therapy to Metformin*

	NESINA 25 mg + Metformin	Placebo + Metformin
A1C (%)	N=203	N=103
Baseline (mean)	7.9	8.0
Change from baseline (adjusted mean†)	-0.6	-0.1
Difference from placebo (adjusted mean† with 95% confidence interval)	-0.5‡ (-0.7, -0.3)	—
% of patients (n/N) achieving A1C ≤7%	44% (92/207)‡	18% (19/104)
Fasting Plasma Glucose (mg/dL)	N=204	N=104
Baseline (mean)	172	180
Change from baseline (adjusted mean†)	-17	0
Difference from placebo (adjusted mean† with 95%confidence interval)	-17‡ (-26, -9)	—

*Intent-to-treat population using last observation on study.
†Least squares means adjusted for treatment, baseline value, geographic region, and baseline metformin dose.
‡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.

Table 7. Glycemic Parameters in a 26-Week Study of NESINA, Pioglitazone, and NESINA in Combination with Pioglitazone when Added to Metformin*

	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
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†)	-0.1	-0.9	-0.8	-0.9	-1.0	-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 NESINA (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†)	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 NESINA (adjusted mean† with 95% confidence interval)	-	-	-	-	-	-19‡ (-29, -10)	-23‡ (-33, -13)	-34‡ (-44, -24)

*Intent-to-treat population using last observation on study.
†Least squares means adjusted for treatment, geographic region, metformin dose and baseline value.
‡p≤0.01 when compared to corresponding doses of pioglitazone and NESINA alone.

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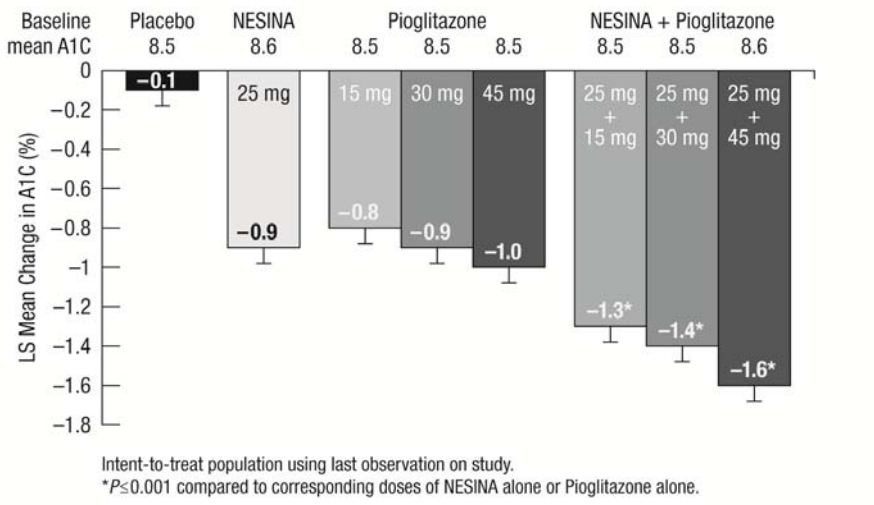
Figure 3. Change From Baseline in A1C at Week 26 with NESINA and Pioglitazone Alone and NESINA in Combination with Pioglitazone When Added to Metformin



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

Add-On Therapy to a Thiazolidinedione

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

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

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

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

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

Table 8. Glycemic Parameters in a 26-Week, Placebo-Controlled Study of NESINA as Add-on Therapy to Pioglitazone*

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

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

Add-on Combination Therapy with Pioglitazone and Metformin

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

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

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

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

Table 9. Glycemic Parameters in a 52-Week, Controlled Study of NESINA as Add-On Combination Therapy With Pioglitazone and Metformin*

	NESINA 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)
Fasting Plasma Glucose (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 + pioglitazone at the 0.025 one-sided significance level.
§ p<0.001 compared to pioglitazone 45 mg + metformin

Add-On Therapy to a Sulfonylurea

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

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

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

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

Table 10. Glycemic Parameters in a 26-Week, Placebo-Controlled Study of NESINA as Add-on Therapy to Glyburide*

	NESINA 25 mg + Glyburide	Placebo + Glyburide
A1C (%)	N=197	N=97
Baseline (mean)	8.1	8.2
Change from baseline (adjusted mean†)	-0.5	0
Difference from placebo (adjusted mean† with 95% confidence interval)	-0.5‡ (-0.7, -0.3)	—
% of patients (n/N) achieving A1C ≤7%	35% (69/198)‡	18% (18/99)
Fasting Plasma Glucose (mg/dL)	N=198	N=99
Baseline (mean)	174	177
Change from baseline (adjusted mean†)	-8	2
Difference from placebo (adjusted mean† with 95% confidence interval)	-11 (-22, 1)	—

*Intent-to-treat population using last observation on study.
†Least squares means adjusted for treatment, baseline value, geographic region, and baseline glyburide dose.
‡p<0.01 compared to placebo.

Add-On Therapy to Insulin

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

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

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

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

Table 11. Glycemic Parameters in a 26-Week, Placebo-Controlled Study of NESINA as Add-on Therapy to Insulin*

	NESINA 25 mg + Insulin ± Metformin	**Placebo + Insulin ± Metformin**
A1C (%)	N=126	N=126
Baseline (mean)	9.3	9.3
Change from baseline (adjusted mean†)	-0.7	-0.1
Difference from placebo (adjusted mean† with 95% confidence interval)	-0.6‡ (-0.8, -0.4)	—
% of patients (n/N) achieving A1C ≤7%	8% (10/129)	1% (1/129)
Fasting Plasma Glucose (mg/dL)	N=128	N=127
Baseline (mean)	186	196
Change from baseline (adjusted mean†)	-12	6
Difference from placebo (adjusted mean† with 95% confidence interval)	-18‡ (-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.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

12.5 mg tablet: yellow, oval, biconvex, film-coated, with “TAK ALG-12.5” printed on one 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

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

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

Storage

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

17.1 Instructions

Inform patients of the potential risks and benefits of NESINA.

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

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

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

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

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

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

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614 **MEDICATION GUIDE**

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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
  - sweating
  - fast heartbeat
  - 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 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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