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

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

Warnings and Precautions (5.5) 8/2015

----------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)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.5)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with NESINA or any other antidiabetic drug. (5.6)

----------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: 8/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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.

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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 nonfatal 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.

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5.5 Severe and Disabling Arthralgia

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

5.6 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 seven 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.

Four placebo-controlled and one active-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)

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

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

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

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

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