PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrNESINA®

alogliptin (as alogliptin benzoate)

6.25 mg, 12.5 mg and 25 mg tablets

ATC Code: A10BH04
Dipeptidyl peptidase 4 (DPP-4) inhibitors

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 6.25 mg, 12.5 mg, and 25 mg	For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section

INDICATIONS AND CLINICAL USE

NESINA® is indicated to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM)

- as monotherapy as an adjunct to diet and exercise in patients for whom metformin is inappropriate due to contraindications or intolerance
- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control
- in combination with a sulfonylurea (SU) when diet and exercise plus a SU alone do not provide adequate glycemic control
- in combination with pioglitazone when diet and exercise plus pioglitazone alone do not provide adequate glycemic control
- in combination with pioglitazone and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycemic control
- in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin (with or without metformin) do not provide adequate glycemic control

Geriatrics (≥ 65 years of age): No dose adjustment is necessary based on age. However, dosing of NESINA® should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dosage adjustment should be based on an assessment of renal function (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age): The safety and efficacy of NESINA® in pediatric patients have not been established. Therefore, NESINA® should not be used in this population.

CONTRAINDICATIONS

NESINA® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

General

NESINA® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Cardiovascular

There is limited experience with NESINA® therapy in patients with congestive heart failure of New York Heart Association (NYHA) functional classes III and IV. NESINA® should therefore, be used with caution in these patients (see ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

Hepatic

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).

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® has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9) and is therefore, not recommended for use in such patients (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pancreatitis

Events of acute pancreatitis have been reported with NESINA® in clinical trials and in postmarketing reports. Reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, were noted in patients taking NESINA® and other members of this class.

After initiation of NESINA®, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, NESINA® should be promptly discontinued and appropriate management should be initiated (see ADVERSE REACTIONS).

Hypersensitivity Reactions

Postmarketing events of serious hypersensitivity reactions in patients treated with NESINA® such as anaphylaxis, angioedema, and severe cutaneous adverse reactions including Stevens-Johnson syndrome have been reported and have been associated with other DPP-4 inhibitors. A single event of serum sickness was observed with NESINA® treatment in a clinical trial. If a hypersensitivity reaction is suspected, discontinuation of NESINA® should be considered. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor, since it is unknown whether such patients will be predisposed to angioedema with NESINA®.

Hypoglycemia

As sulfonylureas and insulin are each known to cause hypoglycemia, a lower dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycemia when these drugs are used in combination with NESINA® (see DOSAGE AND ADMINISTRATION).

Caution should be exercised when NESINA® is used in combination with metformin and pioglitazone, as an increased risk of hypoglycemia has been observed with this regimen.

Skin

Bullous pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of NESINA® and other DPP-4 inhibitors. In reported cases, patients typically recovered with topical or systemic immunosuppresive treatment and discontinuation of the DPP-4 inhbitor.

Tell patients to immediately report development of blisters or erosions while receiving NESINA®. If bullous pemphigoid is suspected, NESINA® should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Renal

As there is a need for dose adjustment in patients with moderate or severe renal impairment, or End-Stage Renal Disease (ESRD) requiring dialysis, assessment of renal function is recommended prior to initiation of NESINA® and periodically thereafter (see DOSAGE AND ADMINISTRATION).

Experience in patients with severe renal impairment or ESRD requiring dialysis is limited and NESINA® should be used with caution in such patients (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Special Populations

Pregnant Women
There are no adequate or well-controlled studies in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to developmental toxicity (see TOXICOLOGY). As a precautionary measure, NESINA® should not be used during pregnancy.

Nursing Women
It is unknown whether NESINA® is excreted in human milk. Alogliptin is secreted in the milk of lactating rats. A risk to the breast-fed child cannot be excluded. NESINA® should not be used by a woman who is nursing.

Pediatrics (< 18 years of age):
Safety and effectiveness of NESINA® in pediatric patients under 18 years of age have not been established. Therefore, NESINA® should not be used in this population.

Geriatrics (> 65 years of age)
No dose adjustment is necessary based on age. However, dosing of NESINA® should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dosage adjustment should be based on an assessment of renal function (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests
Response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is especially useful for evaluating long-term glycemic control.

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.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

NESINA® was generally well-tolerated in controlled clinical studies. The most common adverse events in patients treated with alogliptin 25 mg were headache (5.7%), upper respiratory tract infection (5.7%) and nasopharyngitis (5.6%).

The incidence of serious adverse events was low in both treatment groups (alogliptin 25 mg 5.7 % vs 3.2 % placebo). The most frequently reported treatment-related serious adverse event in patients treated with alogliptin 25 mg was hypoglycemia (0.12%). The main causes for discontinuation for NESINA® 25 mg occurring more frequently than in placebo were decreased creatinine renal clearance (0.6%), increased blood creatinine (0.2%), renal impairment (0.2%); vomiting (0.1%); peripheral oedema (0.1%); anxiety (0.1%); and cardiac failure congestive (<0.1%)

Pancreatitis
In a pooled analysis of 14 Phase 2 and 3 studies, including a cardiovascular outcomes trial, pancreatitis was reported in 11 of 5902 (0.2%) patients receiving NESINA 25 mg daily, compared to 5 of 5183 (<0.1%) patients receiving all comparators (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic). In the completed cardiovascular outcomes study, pancreatitis was reported for 10 (0.4%) subjects in the alogliptin group and 7 (0.3%) subjects in the placebo group, which equates to reporting rates of 3 and 2 events per 1000 years with alogliptin and placebo, respectively.

Serious Hypersensitivity Reactions
Serious cutaneous events and a single event of serum sickness were reported with patients administering therapeutic doses of NESINA® in clinical trials. Post-market events of anaphylaxis, angioedema, and severe cutaneous adverse reactions including Stevens-Johnson syndrome have been reported with NESINA® (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions).

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A total of 9405 patients with type 2 diabetes mellitus, including 3750 patients treated with 25 mg NESINA® and 2476 patients treated with 12.5 mg NESINA®, participated in one Phase 2 or 12 Phase 3 double-blind, placebo- or active-controlled clinical studies. In addition, a cardiovascular outcomes study with 5380 patients with type 2 diabetes mellitus and a recent acute coronary syndrome event was conducted with 2701 randomized to alogliptin and 2679 randomized to placebo. These studies evaluated the effects of alogliptin on glycemic control and its safety as monotherapy, as initial combination therapy with metformin or pioglitazone, and as add-on therapy to metformin, or a sulfonylurea, or pioglitazone (with or without metformin or a sulfonylurea), or insulin (with or without metformin).

A pooled analysis of reported adverse reactions regardless of causality in patients treated with NESINA® 25 mg with incidence of ≥1% and greater than the incidence in the placebo group of 13 controlled Phase 2 and 3 studies are presented in Table 1.

Table 1. Treatment Emergent Adverse Events Reported in ≥1% of Patients Treated with NESINA® and More Frequently Than in Patients Given Placebo in Pooled Studies*

System Organ Class/ Preferred Term	Alogliptin 25 mg (N = 3749)	Placebo (N = 793)	Active Comparator (N = 2257)	All Comparators (N = 3050)
Blood and lymphatic system disorders				
Anaemia	74 (2.0%)	9 (1.1%)	53 (2.3%)	62 (2.0%)
Neutropenia	38 (1.0%)	1 (0.1%)	39 (1.7%)	40 (1.3%)
Gastrointestinal disorders				
Abdominal pain	48 (1.3%)	5 (0.6%)	28 (1.2%)	33 (1.1%)
Abdominal pain upper	45 (1.2%)	8 (1.0%)	18 (0.8%)	26 (0.9%)
Constipation	62 (1.7%)	12 (1.5%)	40 (1.8%)	52 (1.7%)
Nausea	89 (2.4%)	17 (2.1%)	50 (2.2%)	67 (2.2%)
Toothache	40 (1.1%)	7 (0.9%)	16 (0.7%)	23 (0.8%)
Vomiting	45 (1.2%)	9 (1.1%)	30 (1.3%)	39 (1.3%)
General disorders and administration site conditions				
Fatigue	49 (1.3%)	9 (1.1%)	37 (1.6%)	46 (1.5%)
Oedema peripheral	91 (2.4%)	16 (2.0%)	57 (2.5%)	73 (2.4%)
Pyrexia	42 (1.1%)	7 (0.9%)	39 (1.7%)	46 (1.5%)
Infections and infestations				
Gastroenteritis	48 (1.3%)	8 (1.0%)	30 (1.3%)	38 (1.2%)
Influenza	105 (2.8%)	17 (2.1%)	86 (3.8%)	103 (3.4%)
Nasopharyngitis	192 (5.1%)	35 (4.4%)	99 (4.4%)	134 (4.4%)
Pharyngitis	60 (1.6%)	9 (1.1%)	31 (1.4%)	40 (1.3%)
Upper respiratory tract infection	196 (5.2%)	36 (4.5%)	95 (4.2%)	131 (4.3%)
Investigations				
C-reactive protein increased	43 (1.1%)	3 (0.4%)	27 (1.2%)	30 (1.0%)

Table 1. Treatment Emergent Adverse Events Reported in ≥1% of Patients Treated with NESINA® and More Frequently Than in Patients Given Placebo in Pooled Studies*

System Organ Class/ Preferred Term	Alogliptin 25 mg (N = 3749)	Placebo (N = 793)	Active Comparator (N = 2257)	All Comparators (N = 3050)
Creatinine renal clearance decreased	58 (1.5%)	4 (0.5%)	41 (1.8%)	45 (1.5%)
Metabolism and nutrition disorders				
Dyslipidaemia	94 (2.5%)	12 (1.5%)	87 (3.9%)	99 (3.2%)
Hypercholesterolaemia	45 (1.2%)	9 (1.1%)	29 (1.3%)	38 (1.2%)
Musculoskeletal and connective tissue disorders				
Arthralgia	102 (2.7%)	20 (2.5%)	72 (3.2%)	92 (3.0%)
Back pain	125 (3.3%)	19 (2.4%)	86 (3.8%)	105 (3.4%)
Muscle spasms	37 (1.0%)	7 (0.9%)	14 (0.6%)	21 (0.7%)
Musculoskeletal pain	38 (1.0%)	7 (0.9%)	28 (1.2%)	35 (1.1%)
Pain in extremity	80 (2.1%)	16 (2.0%)	57 (2.5%)	73 (2.4%)
Nervous system disorders				
Diabetic neuropathy	37 (1.0%)	1 (0.1%)	17 (0.8%)	18 (0.6%)
Headache	203 (5.4%)	30 (3.8%)	113 (5.0%)	143 (4.7%)
Respiratory, thoracic and mediastinal disorders				
Cough	66 (1.8%)	10 (1.3%)	45 (2.0%)	55 (1.8%)
Skin and subcutaneous tissue disorders				
Pruritus	48 (1.3%)	2 (0.3%)	12 (0.5%)	14 (0.5%)
Rash	53 (1.4%)	7 (0.9%)	27 (1.2%)	34 (1.1%)
Vascular disorders				
Hypertension	147 (3.9%)	26 (3.3%)	102 (4.5%)	128 (4.2%)

***** Includes data based on interim (52 week) analysis for Study SYR-322_305

Less Common Clinical Trial Adverse Drug Reactions ≥0.1% and <1% (Drug-Related and Greater than Placebo in Pooled Monotherapy and in Individual Placebo-Controlled Phase 3 Studies)

Blood and lymphatic system disorders: Leukopenia, Lymphocytosis, Neutropenia

Cardiac disorders: Atrial fibrillation, Cardiac failure congestive, Palpitations

Eye disorders: Vision blurred

Gastrointestinal disorders: Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Anal fissure, Constipation, Dyspepsia, Enterocolitis, Gastrointestinal pain, Toothache, Umbilical hernia, Vomiting

General disorders and administration site conditions: Asthenia, Fatigue, Non-cardiac chest pain, Oedema

Immune system disorders: Hypersensitivity, Serum sickness

Infections and infestations: Acute tonsillitis, Bronchitis, Fungal infection, Fungal skin infection, Herpes simplex, Herpes zoster, Nasopharyngitis, Oral herpes

Injury, poisoning and procedural complications: Contusion, Road traffic accident, Scratch

Investigations: Alanine aminotransferase increased, Blood pressure increased, Blood triglycerides increased, Electrocardiogram QT prolonged, Electrocardiogram ST-T segment abnormal, Electrocardiogram T wave abnormal, Electrocardiogram T wave inversion, Hepatic enzyme increased, Liver function test abnormal, Weight increased

Metabolism and nutrition disorders: Decreased appetite, Hypercholesterolaemia, Hypertriglyceridaemia, Hyperuricaemia, Hypoglycemia, Hyponatraemia

Musculoskeletal and connective tissue disorders: Bursitis, Groin pain, Joint stiffness, Muscle contracture, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain

Nervous system disorders: Disturbance in attention, Dysgeusia, Lethargy, Memory impairment, Migraine, Neuropathy peripheral, Paraesthesia, Poor quality sleep, Sciatica, Syncope, Tension headache, Tremor

Psychiatric disorders: Agitation, Loss of libido, Nightmare

Renal and urinary disorders: Albuminuria, Dysuria, Haematuria

Reproductive system and breast disorders: Erectile dysfunction

Respiratory, thoracic and mediastinal disorders: Dyspnoea, Pulmonary embolism

Skin and subcutaneous tissue disorders: Acne, Blister, Dermatitis acneiform, Dermatitis allergic, Dermatitis contact, Drug eruption, Dry skin, Erythema, Hyperhidrosis, Neurodermatitis, Pruritus generalised, Rash (including macular and/or papular), Skin exfoliation, Subcorneal pustular dermatosis

Vascular disorders: Hot flush, Hypertension

Abnormal Hematologic and Clinical Chemistry Findings

Overall, no clinically significant trend in abnormal laboratory findings were seen in patients treated with NESINA® compared with patients treated with placebo or active comparators.

Post-Market Adverse Drug Reactions

Immune system disorders: Hypersensitivity reactions, including anaphylaxis
Gastrointestinal disorders: Acute pancreatitis, gastroesophageal reflux disease
Hepatobiliary disorders: Hepatic dysfunction including hepatic failure
Skin and subcutaneous tissue disorders*:* Exfoliative skin conditions including Stevens-Johnson syndrome, angioedema, urticaria, bullous pemphigoid

DRUG INTERACTIONS

Overview

Alogliptin is primarily excreted unchanged in the urine and metabolism by the cytochrome P450 (CYP) enzyme system is negligible (see PHARMACOKINETICS). In addition, alogliptin does not induce and does not inhibit the major human CYP isoforms at concentrations achieved with the recommended dose of 25 mg alogliptin. As a result, alogliptin is not expected to interact with substances which induce, inhibit or are known substrates of cytochrome P450 enzymes. Furthermore, clinical data suggest that interactions with p-glycoprotein inhibitors are not expected, and no drug-drug interactions were observed with alogliptin and other renally excreted drugs in clinical studies.

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2. Effect of Alogliptin on the Pharmacokinetics of Other Drugs

Common Name	Reference	Effect	Clinical Comments
Atorvastatin	CT	Concomitant administration of alogliptin and atorvastatin (a CYP3A4 substrate) results in a 13% increase in atorvastatin C_{max}, no effect on atorvastatin T_{max}, and a 14% increase in atorvastatin AUC.	No Recommended Dose Adjustment
Cimetidine	CT	Concomitant administration of alogliptin and cimetidine (an organic cation transporter 2 inhibitor) had no effect on cimetidine C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Digoxin	CT	Concomitant administration of alogliptin and digoxin (a Pgp substrate) had no effect on digoxin C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Ethinyl estradiol	CT	Concomitant administration of alogliptin and ethinyl estradiol (a CYP3A4 substrate) had no effect on ethinyl estradiol C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Glyburide	CT	Concomitant administration of alogliptin and glyburide (a CYP2C9	No Recommended Dose Adjustment

		substrate) resulted in a 15% increase in glyburide C_{max} and no effect on glyburide T_{max} and AUC.	
Metformin	CT	Concomitant administration of alogliptin and metformin (an organic cation transporter 2 substrate) results in no effect in metformin C_{max} and T_{max} and a 19% increase in metformin AUC.	No Recommended Dose Adjustment
Norethindrone	CT	Concomitant administration of alogliptin and norethindrone (a CYP3A4 substrate) had no effect on norethindrone C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Pioglitazone	CT	Concomitant administration of alogliptin and pioglitazone (a CYP2C8 substrate) had no effect on pioglitazone C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Warfarin	CT	Concomitant administration of alogliptin and warfarin (a CYP1A2/2C9 substrate) had no effect on R- and S-warfarin C_{max}, T_{max}, and AUC and pharmacodynamics (PT or INR).	No Recommended Dose Adjustment
Caffeine, Midazolam, Tolbutamide, Dextromethorphan, Fexofenadine Cocktail	CT	Concomitant administration had no effect on caffeine (CYP1A2 substrate), tolbutamide (CYP2C9 substrate), or midazolam (CYP3A4 substrate) C_{max}, T_{max}, and AUC. Concomitant administration results in a 32% increase in dextromethorphan (CYP2D6 substrate) C_{max}, no effect on dextromethorphan T_{max}, and a 27% increase in dextromethorphan AUC. Concomitant administration results in a 17% increase in fexofenadine (Pgp substrate) C_{max}, no effect on fexofenadine T_{max}, and a 34% increase in fexofenadine AUC.	No Recommended Dose Adjustment
CT = Clinical Trial; C: Case Study; T = Theoretical			

Table 3. Effect of Other Drugs on the Pharmacokinetics of Alogliptin

Common Name	Reference	Effect	Clinical Comments
Atorvastatin	CT	Concomitant administration of alogliptin and atorvastatin (a CYP3A4 substrate) had no effect on alogliptin C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Cimetidine	CT	Concomitant administration of alogliptin and cimetidine (an organic cation transporter 2 inhibitor) had no effect on alogliptin C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Cyclosporine	CT	Concomitant administration of alogliptin and cyclosporine (a Pgp	No Recommended Dose Adjustment

		inhibitor) had no effect on alogliptin C_{max}, T_{max}, and AUC.	
Digoxin	CT	Concomitant administration of alogliptin and digoxin (a Pgp substrate) had no effect on alogliptin C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Fluconazole	CT	Concomitant administration of alogliptin and fluconazole (a CYP2C9 inhibitor) resulted in a 20% decrease in alogliptin C_{max}, delay of alogliptin T_{max} by 1.5 hr, and no effect on alogliptin AUC.	No Recommended Dose Adjustment
Gemfibrozil	CT	Concomitant administration of alogliptin and gemfibrozil (a CYP2C8/9 inhibitor) resulted in a 15% decrease in alogliptin C_{max}, delay of alogliptin T_{max} by 2 hr, and no effect on alogliptin AUC.	No Recommended Dose Adjustment
Ketoconazole	CT	Concomitant administration of alogliptin and ketoconazole (a CYP3A4 inhibitor) resulted in a 22% increase in alogliptin C_{max} and no effect on alogliptin T_{max} and AUC.	No Recommended Dose Adjustment
Metformin	CT	Concomitant administration of alogliptin and metformin (an organic cation transporter 2 substrate) had no effect on alogliptin C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Pioglitazone	CT	Concomitant administration of alogliptin and pioglitazone (a CYP2C8 substrate) had no effect on alogliptin C_{max}, T_{max}, and AUC.	No Recommended Dose Adjustment
Voglibose	CT	Concomitant administration of alogliptin and voglibose (an alpha-glucosidase inhibitor) results in a 10% decrease in alogliptin C_{max}, no effect on alogliptin T_{max}, and a 22% decrease in alogliptin AUC.	No Recommended Dose Adjustment
CT = Clinical Trial; C: Case Study; T = Theoretical			

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

No specific studies on the effects of NESINA® on the ability to drive and use machines have

been performed.

When NESINA® is used in combination with pioglitazone and metformin or in combination with insulin or sulfonylurea, patients should be advised to take precautions to avoid hypoglycemia while driving or using machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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 (see WARNINGS AND PRECAUTIONS, Renal).

When NESINA® is used in combination with a sulfonylurea or insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS).

Caution should be exercised when NESINA® is used in combination with metformin and pioglitazone, as an increased risk of hypoglycemia has been observed with this regimen.

NESINA® can be administered with or without food.

Recommended Dose and Dosage Adjustment

The recommended dose of NESINA® is 25 mg once daily as monotherapy, add-on therapy to metformin and/or pioglitazone, or a sulfonylurea, or insulin.

Special Populations

Geriatrics

No dose adjustment is necessary based on age. However, dosing of NESINA® should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dosage adjustment should be based on an assessment of renal function (see WARNINGS AND PRECAUTIONS).

Pediatrics

The safety and efficacy of NESINA® in pediatric patients have not been established. Therefore, NESINA® should not be used in this population.

Hepatic Impairment

No dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh scores of 5 to 9). NESINA® has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9) and is therefore, not recommended for use in such patients (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment
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 (see WARNINGS AND PRECAUTIONS, Renal).

No dosage adjustment of NESINA® is required in patients with mild renal function.

The dose of NESINA® is 12.5 mg once daily for patients with moderate renal impairment.

The dose of NESINA® is 6.25 mg once daily for patients with severe renal impairment or End-Stage Renal Disease (ESRD) requiring hemodialysis. NESINA® may be administered without regard to the timing of dialysis. Experience in patients requiring renal dialysis is limited. NESINA® has not been studied in patients undergoing peritoneal dialysis (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Missed Dose
If a dose is missed, NESINA® should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Administration
NESINA® should be taken once daily with or without food. The tablets should be swallowed whole with water.

OVERDOSAGE

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

Management
In the event of an overdose, clinical monitoring and supportive measures should be employed, as dictated by the patient's clinical status.

Minimal quantities of NESINA® are removed by hemodialysis (approximately 7% of the drug was removed during a 3-hour hemodialysis session). Therefore, hemodialysis is of little benefit in an overdose situation. It is not known if NESINA® is removed by peritoneal dialysis.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (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 potent, reversible and selective inhibitor of dipeptidyl peptidase-4 (DPP-4) that slows the inactivation of the incretin hormones, thereby increasing their concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus. In summary, alogliptin is expected to improve glycemic control by inhibiting DPP-4 activity.

Alogliptin does not inhibit the activity of other closely related enzymes *in vitro* at concentrations 15 fold greater than the mean human plasma exposure at the recommended clinical dose. Alogliptin (mean IC50 = 6.9) is greater than 10,000 fold more selective for DPP-4 than other related enzymes including DPP-8 and DPP-9.

Pharmacodynamics

Administration of 25 mg alogliptin to patients with type 2 diabetes mellitus produced peak inhibition of DPP-4 within 1 to 2 hours and exceeded 93% both after a single 25 mg dose and after 14 days of once-daily dosing. Inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing. The 4-hour postprandial glucose concentrations were consistently reduced from baseline following breakfast, lunch and dinner. When these glucose concentrations were averaged across all 3 meals and corrected from baseline, 14 days of treatment with 25 mg alogliptin resulted in a mean reduction in 4-hour post prandial glucose compared to placebo (-1.30 mmol/L vs 0.65 mmol/L, respectively).

Cardiac Electrophysiology: In a single-blind, randomised, placebo- and positive-controlled, parallel group ECG assessment study, healthy subjects received alogliptin 50 mg once daily (N=62), alogliptin 400 mg once daily (N=62), or placebo (N=63) for 7 days. ECG data were collected at baseline and on Days 1 and 7 of treatment at 0 hour and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hour post-dose. In the alogliptin 50 mg group, the maximum mean difference from placebo in the QTcF interval was 4.5 ms (90% CI 0.4, 8.5) at 2 hour post-dosing on Day 7 of treatment. In the alogliptin 400 mg treatment group, the maximum mean difference from placebo was 5.8 ms (90% CI 1.8, 9.7) at 1 hour post-dosing on Day 7 of treatment. The therapeutic 25 mg dose of alogliptin was not tested in this study; however, based on pharmacokinetic-pharmacodynamic modelling, no QTcF prolongation is predicted at the 25 mg dose, assuming a mean steady-state C_{max} of 152.78 ng/mL. No effects on heart rate or the QRS duration were observed at the 50 mg and 400 mg doses tested in this study.

Pharmacokinetics

The pharmacokinetics of alogliptin have been studied in healthy subjects and in patients with type 2 diabetes mellitus (Table 4), and were comparable between the two populations.

Table 4. Summary of Alogliptin Steady State Pharmacokinetic Parameters (Arithmetic Mean ± SD) in Patients with T2DM

	T_{max}* (hr)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	$AUC_{(0-24)}$ (ng·hr/mL)	Clearance (L/hr)	Volume of Distribution (L)
Alogliptin 25 mg at Steady State in Patients with T2DM	**1.1 (0.8, 4.5)**	**153 ± 39**	**21.1 ± 8.8**	**1474 ± 214**	**10.4 ± 2.3**	**299 ± 77**

* T_{max} is presented as Median (Min, Max).

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%.

Absorption
The absolute bioavailability of alogliptin is approximately 100%.

Administration with a high-fat meal resulted in no change in total and peak exposure to alogliptin. NESINA® may, therefore, be administered with or without food.

Distribution
Following a single intravenous dose of 12.5 mg 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 alogliptin, 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 a highly selective inhibitor of DPP-4 similar to alogliptin; 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 therapeutic doses.

Elimination

Following administration of an oral dose of [^{14}C] alogliptin, 76% of total radioactivity was eliminated in the urine and involved some active renal tubular secretion, and 13% was 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. Systemic clearance of alogliptin was 14.0 L/hr.

Linearity and Time dependency
Total and peak exposure to alogliptin increased proportionately across single doses of 6.25 mg up to 100 mg alogliptin (covering the therapeutic dose range).

Total exposure ($AUC_{(0\text{-}inf)}$) to alogliptin following administration of a single dose was similar to exposure during one dose interval ($AUC_{(0\text{-}24)}$) after 6 or 7 days of once daily dosing between the doses of 25 mg to 400 mg. This indicates no time-dependency in the kinetics of alogliptin after multiple dosing.

Special Populations and Conditions

Pediatrics
The pharmacokinetics of alogliptin in patients <18 years old have not yet been established.

Geriatrics
Pharmacokinetics of alogliptin do not differ significantly between young (age range 18 to 45) and elderly (age range 65 to 85) subjects. No dose adjustment is necessary based on age. However, dosing of NESINA® should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dosage adjustment should be based on an assessment of renal function (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Gender
Pharmacokinetics of alogliptin do not differ significantly between males and females. No dose adjustment is necessary based on gender.

Race
Pharmacokinetics of alogliptin do not differ significantly between the white, black, and Asian populations. No dose adjustment is necessary based on race.

Body Weight
Body weight is unlikely to have a clinically meaningful impact on exposure to alogliptin. No dose adjustment is necessary based on body weight.

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 control subjects. The magnitude of these reductions was not considered to

be clinically meaningful. Therefore, no dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh scores of 5 to 9). Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh score >9, see WARNINGS AND PRECAUTIONS).

Renal Impairment
A single-dose of 50 mg alogliptin was administered to 4 groups of patients with varying degrees of renal impairment (creatinine clearance (CrCl) using the Cockcroft-Gault formula): mild (CrCl = >50 to ≤80 ml/min), moderate (CrCl = ≥30 to ≤50 ml/min), severe (CrCl = <30 ml/min) and End-Stage Renal Disease (ESRD) on haemodialysis.

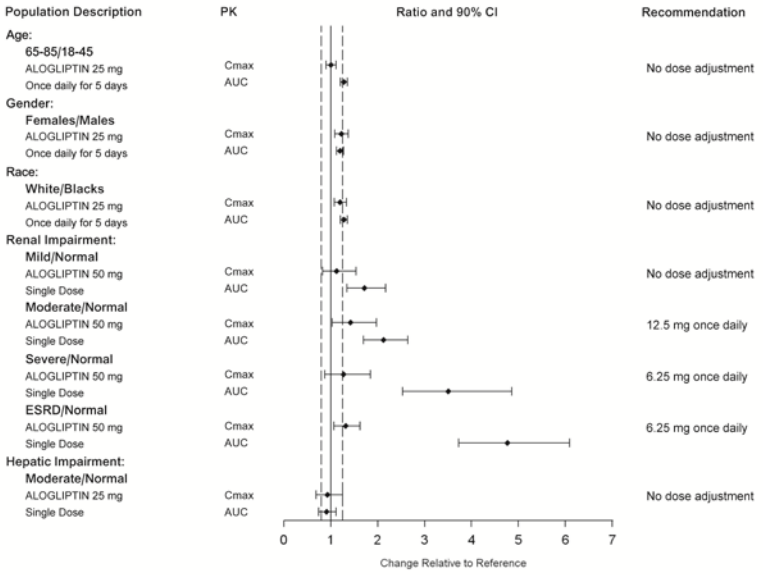
An approximate 1.7-fold increase in AUC for alogliptin was observed in patients with mild renal impairment. However, as the distribution of AUC values for alogliptin in these patients was within the same range as control subjects, no dose adjustment for patients with mild renal impairment is necessary (see WARNINGS AND PRECAUTIONS).

In patients with moderate renal impairment, 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 and end-stage renal disease (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 (see WARNINGS AND PRECAUTIONS).

Genetic Polymorphism
The effect of genetic polymorphisms on the pharmacokinetics of alogliptin has not been studied, as alogliptin is not extensively metabolized and the majority is excreted unchanged in the urine.

Figure 1. Effect of Intrinsic Factors on Exposure to Alogliptin



SPECIAL HANDLING INSTRUCTIONS

There are no special requirements for NESINA®.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NESINA® is supplied as film-coated tablets as follows:

6.25 mg: Light pink, oval, biconvex, film-coated tablets with “TAK” and “ALG-6.25” printed in grey ink on one side.

12.5 mg: Yellow, oval, biconvex, film-coated tablets with “TAK” and “ALG-12.5” printed in grey ink on one side.

25 mg: Light red, oval, biconvex, film-coated tablets with “TAK” and “ALG-25” printed in grey ink on one side.

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 2910, titanium dioxide, ferric oxide (red or yellow), and polyethylene glycol (Macrogol 8000), and is marked with printing ink (Gray F1).

NESINA® tablets are supplied in high-density polyethylene (HDPE) bottles of 30 count tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

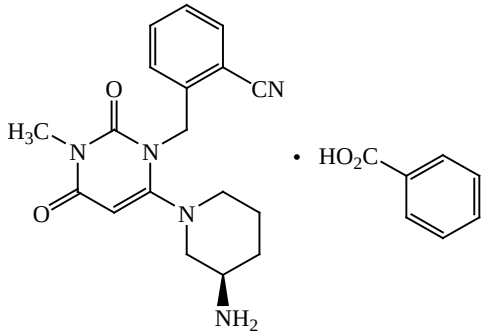
Drug Substance: Alogliptin benzoate

Proper name: alogliptin benzoate

Chemical name: 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl) benzonitrile monobenzoate

Molecular formula and molecular mass: $C_{18}H_{21}N_5O_2 \bullet C_7H_6O_2$
461.51 (benzoate salt) 339.39 (free base)

Structural formula:



Physicochemical properties: 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 methanol, water, and aqueous solutions across the physiologic pH range; slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate.

CLINICAL TRIALS

Study demographics and trial design

Table 5. Summary of patient demographics in pivotal clinical trials

Study #	Trial design	Dosage (patients enrolled/completing the trial), route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (M- Male F- Female)
SYR-322-SULF-007	Phase 3, randomized, double-blinded, placebo-controlled, 3-treatment arm Efficacy (HbA1c)	Glyburide with: ALO 12.5 mg (203/153) ALO 25 mg (198/148) PBO (99/62) Total (500/363) Oral administration Treatment duration: 26 weeks Subjects with T2DM being treated with an SU alone and who were experiencing inadequate glycemic control	500	56.6 (21-80) years	261 (52.2%) Men, 239 (47.8%) Women
SYR-322-MET-008	Phase 3, randomized, double-blinded, placebo-controlled, 3-treatment arm design Efficacy (HbA1c)	MET with: ALO 12.5 mg (213/176) ALO 25 mg (207/165) PBO (104/72) Total (524/413) Oral administration Treatment duration: 26 weeks Subjects with T2DM being treated with MET alone	527	54.7 (22-80) years	265 (50.3%) Men, 262 (49.7%) Women
SYR-322-TZD-009	Phase 3, randomized, double-blinded, placebo-controlled, 3-treatment arm Efficacy (HbA1c)	PIO+SU or MET with: ALO 12.5 mg (197/153) ALO 25 mg (199/160) PBO (97/71) Total (493/384) Oral administration Treatment duration: 26 weeks Subjects with T2DM being treated with a TZD (PIO) alone or in combination with MET or an SU	493	55.4 (24-80) years	287 (58.2%) Men, 206 (41.8%) Women

Table 5. Summary of patient demographics in pivotal clinical trials

Study #	Trial design	Dosage (patients enrolled/completing the trial), route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (M- Male F- Female)
SYR-322-PLC-010	Phase 3, randomized, double-blinded, placebo-controlled, 3-treatment arm Efficacy (HbA1c)	ALO 12.5 mg (133/105) ALO 25 mg (131/107) PBO (64/40) Total (328/252) Oral administration Treatment duration: 26 weeks Subjects with T2DM experiencing inadequate glycemic control on diet and exercise alone	329	53.4 (24-80) years	175 (53.2%) Men, 154 (46.8%) Women
SYR-322-INS-011	Phase 3, randomized, double-blinded, placebo-controlled, 3-treatment arm Efficacy (HbA1c)	Insulin with/without MET with: ALO 12.5 mg (131/83) ALO 25 mg (129/77) PBO (129/55) Total (389/215) Oral administration Treatment duration: 26 weeks Subjects with T2DM being treated with insulin alone or in combination with MET	390	55.4 (23-80) years	229 (58.7%) Women, 161 (41.3%) Men
01-06-TL-322OPI-004	Phase 3, randomized, double-blinded, 2-treatment arm Efficacy (HbA1c)	MET+ALO 25+PIO 30 mg (404/283) MET+PIO 45 mg (399/243) Total (803/526) Oral administration Treatment duration: 52 weeks Subjects with T2DM and inadequate glycemic control on MET (≥1500 mg or MTD) and PIO 30 mg	803	55.1 (25-80) years	389 (48.4%) Women, 414 (51.6%) Men

Table 5. Summary of patient demographics in pivotal clinical trials

Study #	Trial design	Dosage (patients enrolled/completing the trial), route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (M- Male F- Female)
SYR-322_305 (ENDURE)	Phase 3, randomized, double-blinded, active comparator Efficacy (HbA1c)	MET+ALO 12.5 mg (880/472) MET+ALO 25 mg (885/493) MET+Glipizide (874/427) Total (2639/1392) Oral administration Treatment duration: 52 weeks and 104 weeks Subjects with T2DM and inadequate glycemic control on MET ≥1500 mg (or MTD) alone	2639	55.4 (21-80) years	1312 (49.7%) Men, 1327 (50.3%) Women
SYR-322_402 (EXAMINE)	Phase 3b, randomized, double-blinded, placebo-controlled, 2-treatment arm Safety (time from randomization to the first occurrence of any event in the primary MACE composite [CV death, nonfatal MI, and nonfatal stroke])	ALO (25 mg, 12.5 mg, and 6.25 mg QD based on renal function) versus matching placebo Oral administration Treatment duration: mean 17 months; Study participation: mean 19 months Subjects with T2DM and recent ACS	5380	60.9 (26-91) years	3651 (67.9%) Men, 1729 (32.1%) Women

Study Results:

Alogliptin has been studied as monotherapy and as add-on therapy to metformin, or a sulfonylurea, or pioglitazone (with or without metformin or a sulfonylurea), or insulin (with or without metformin).

A total of 14 779 patients with type 2 diabetes mellitus participated in one Phase 2 or 13 Phase 3 (including the cardiovascular outcomes study) double-blind, placebo- or active-controlled clinical studies conducted to evaluate the effects of alogliptin on glycemic control and its safety. In these studies, 2257 (24.9%) alogliptin-treated patients were ≥65 years old and 386 (4.3%) alogliptin-treated patients were ≥75 years old. The studies included 5744 patients with mild renal impairment, 1290 patients with moderate renal impairment, and 82 patients with severe renal

impairment treated with alogliptin. Excluding the cardiovascular outcomes study, 3750 patients were treated with 25 mg alogliptin and 2476 patients were treated with alogliptin 12.5 mg.

Overall, treatment with the recommended daily dose of 25 mg alogliptin improved glycemic control when given as monotherapy and as initial or add-on combination therapy. This was determined by clinically relevant and statistically significant reductions in glycosylated hemoglobin (HbA1c) compared to control from baseline to study endpoint. Reductions in HbA1c were similar across different subgroups including mild to moderate renal impairment, age, gender, race and body mass index (BMI). Clinically meaningful reductions in HbA1c compared to control were also observed with 25 mg alogliptin regardless of baseline background medication dose, for subjects with a baseline HbA1c >7.5. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Generally, the effects of alogliptin on body weight and lipids were neutral.

Alogliptin as Monotherapy (SYR-322-PLC-010)

Treatment with NESINA® 25 mg resulted in statistically significant improvements from baseline in HbA1c as early as Week 4 (Figure 2) and fasting plasma glucose (FPG) as early as Week 1 compared to placebo at Week 26 (Table 6). Fewer patients receiving NESINA® 25 mg (8%) required hyperglycemic rescue compared with those receiving placebo (30%) during the study. Body weight did not differ significantly between the groups.

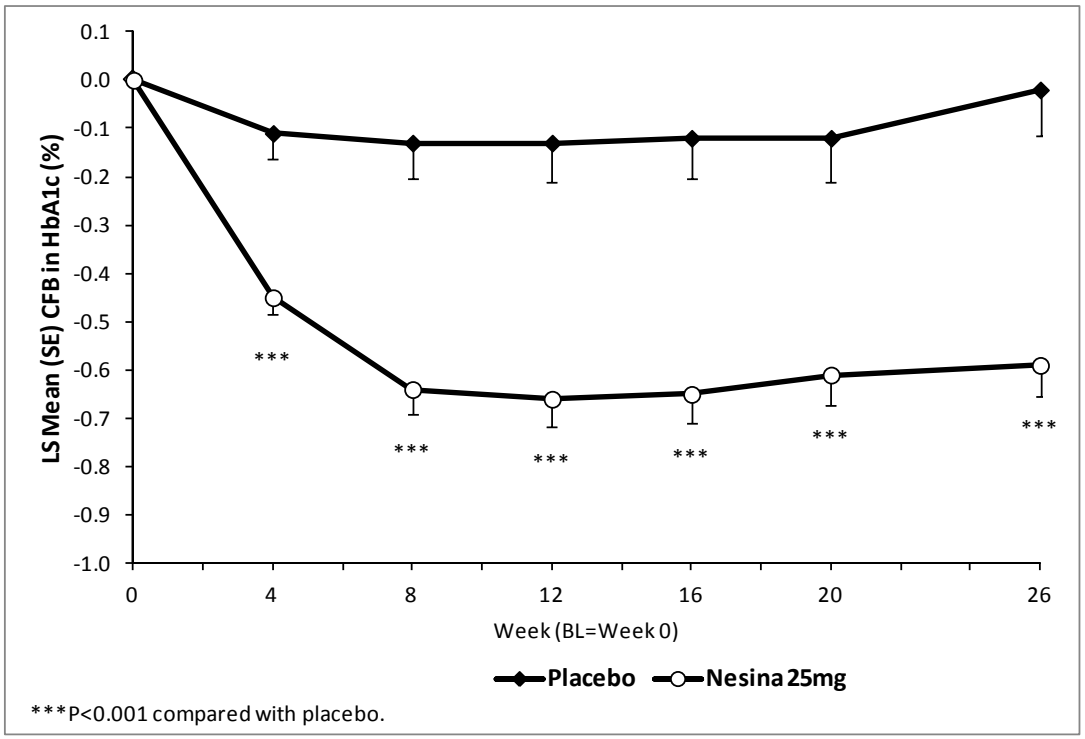
Table 6. Glycemic Parameters in 26-week Placebo-controlled Monotherapy Study of NESINA® in Patients with Type 2 Diabetes (SYR-322-PLC-010)

	NESINA® 25 mg	**Placebo**
$HbA1_c$ (%)	**N=131**	**N=64**
Baseline (mean)	7.91	8.03
Change from Baseline at Week 26†	-0.59 ± 0.066 (n=128)	-0.02 ± 0.094 (n=63)
Difference vs. Placebo†	-0.57% * [-0.80, -0.35]	
Patients (%) achieving HbA1c ≤7% at Week 26	44.3	23.4
FPG (mmol/L)	**N=129**	**N=64**
Baseline (mean)	9.55	9.62
Change from Baseline at Week 26†	-0.9 ± 0.2 (n=129)	0.6 ± 5.24 (n=64)
Difference vs. Placebo†	1.54 mmol/L * [-2.24, -0.84]	

† Least squares mean ± S.E.

* p<0.001, [ ] shows two-sided 95% confidence interval

Figure 2. Change from Baseline at Week 26 in HbA1c with NESINA® 25 mg as Monotherapy



Alogliptin as Add-on Therapy to Metformin (SYR-322-MET-008)

The addition of NESINA® 25 mg once daily to metformin therapy (mean dose = 1847 mg) resulted in statistically significant improvements from baseline in HbA1c and FPG at Week 26 when compared to the addition of placebo (Table 7). Significant improvements in HbA1c vs. the addition of placebo were noted as early as 4 weeks after the start of NESINA®, and these remained significant at every time point until Week 26. Significant improvements in FPG vs. placebo were noted as early as 1 week after the start of NESINA®, and these improvements in FPG remained significant at every time point until Week 26. Body weight did not differ significantly between the groups.

Fewer patients receiving 25 mg alogliptin (8.2%) required hyperglycemic rescue compared to those receiving placebo (24.0%) during the study.

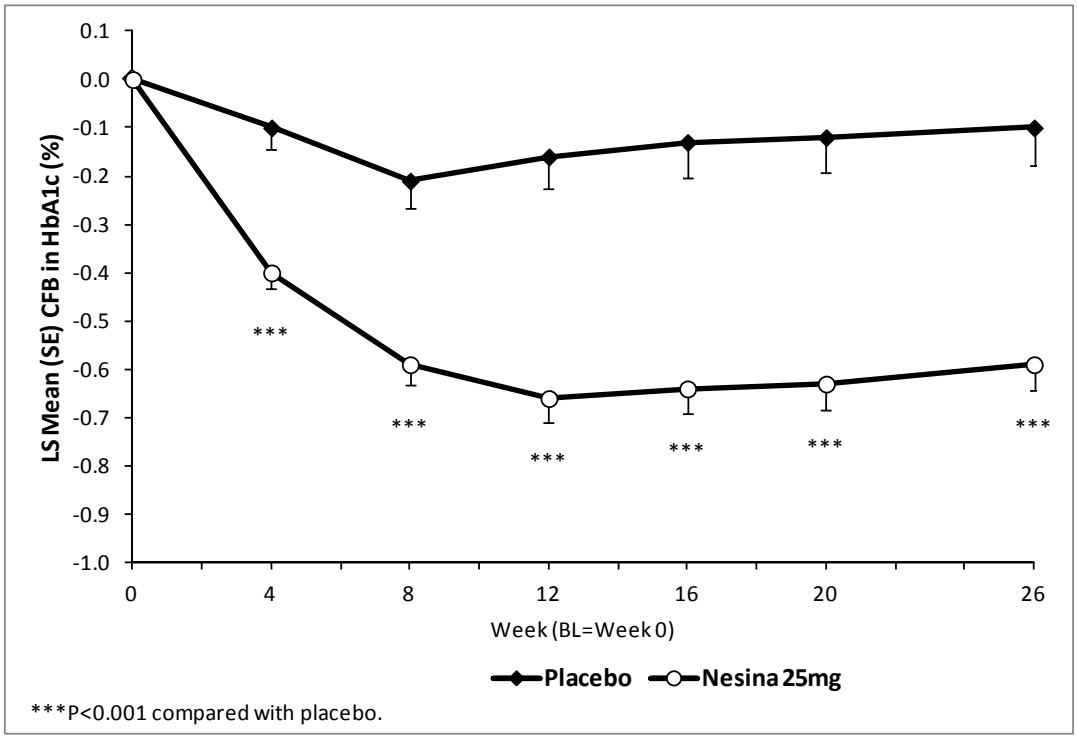
Table 7. Glycemic Parameters at Week 26 (Study SYR-322_008)

	NESINA® 25 mg	**Placebo**
$HbA1_c$ (%)	**N=207**	**N=104**
Baseline (mean)	7.93	8.01
Change from Baseline at Week 26†	-0.59 ± 0.054 (n=203)	-0.10 ± 0.076 (n=103)

Difference vs. Placebo†	-0.48% * [-0.67, -0.30]	
Patients (%) achieving HbA1c ≤7% at Week 26	44.4%	18.3%
FPG (mmol/L)	**N=204**	**N=104**
Baseline (mean)	9.54	9.96
Change from Baseline at Week 26†	-0.97 ± 0.14 (n=204)	0.0 ± 0.20 (n=104)
Difference vs. Placebo†	-0.97 mmol/L * [-1.44, -0.49]	

†Least squares mean ± S.E.
* p<0.001, [ ] shows two-sided 95% confidence interval

Figure 3. Change from Baseline at Week 26 in HbA1c When NESINA® 25 mg is added to Metformin



*Alogliptin as Add-on Therapy to Metformin vs Glipizide Add-on to Metformin (*SYR-322_305) ENDURE

In a 104 week study to evaluate durability of glycemic control, patients were randomized to the addition of either NESINA® 25 mg daily (n = 885), NESINA®12.5 mg daily (n = 880) or glipizide (n = 874) to a background of metformin. Patients receiving glipizide were given an initial dosage of 5 mg/day. After at least 2 weeks, patients receiving glipizide who demonstrated persistent hyperglycemia (FPG ≥13.9 mmol/L) could be up-titrated by the investigator in 5 mg increments in 4-week intervals, up to a maximum of 20 mg per day, over the following

18 weeks. Thereafter, the glipizide dose was to have been maintained for the remainder of the trial. The mean daily dose of glipizide following the titration period was 5.2 mg/day.

The addition of NESINA® 25 mg once daily to metformin therapy (mean dose = 1835 mg) resulted in improvements from baseline in HbA1c at Week 52 and Week 104 that were statistically non-inferior to those produced by glipizide plus metformin therapy (mean dose = 1824 mg). Based on 537 per-protocol patients in the NESINA® 25 mg plus metformin group and 509 per-protocol patients in the glipizide plus metformin group at Week 52, using the last observation carried forward (LOCF), the mean decrease from baseline HbA1c was -0.61% with NESINA® 25 mg and -0.52% with glipizide. These results were maintained at week 104. Results of secondary endpoints, based on the Full Analysis Set assessed at Week 104 (LOCF) showed that the mean change from baseline in FPG was -0.18 mmol/L with NESINA® 25 mg and 0.30 mmol/L with glipizide. Alogliptin did not have any meaningful change on body weight up to Week 104.

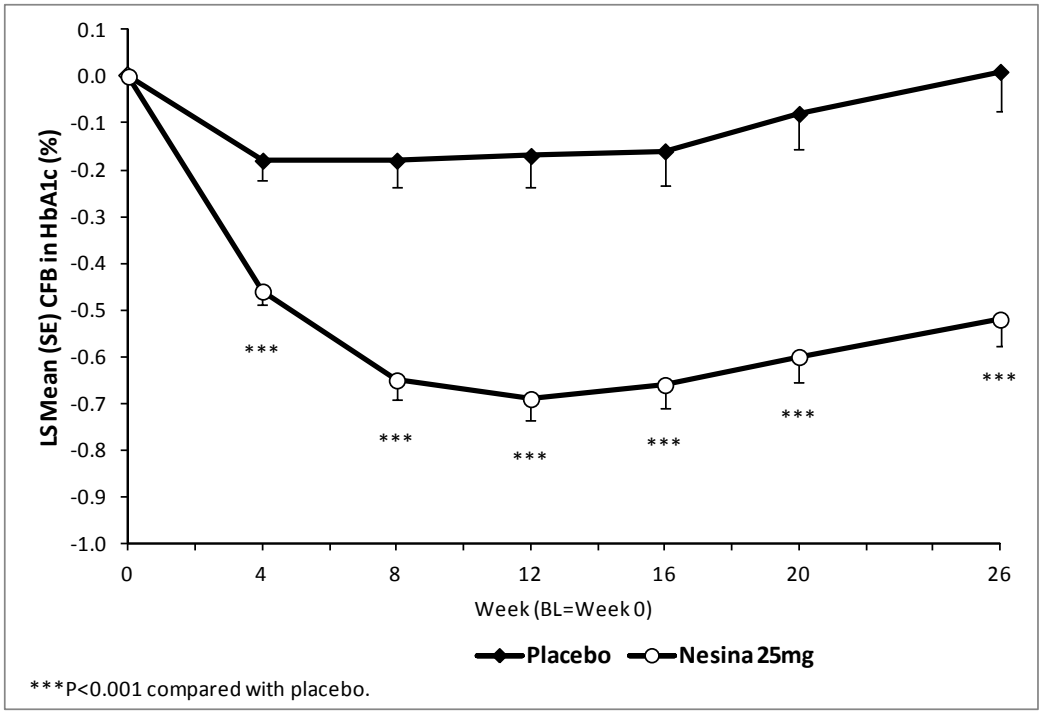
Alogliptin as Add-on Therapy to a Sulfonylurea (SU) (SYR-322-SULF-007)
The addition of 25 mg alogliptin once daily to glyburide therapy (mean dose = 12.2 mg) resulted in statistically significant improvements from baseline in HbA1c (see Figure 4) at Week 26 when compared to the addition of placebo (Table 8). No significant differences from placebo were noted for mean change from baseline in FPG at Week 26 (25 mg alogliptin showed a reduction of 0.47 mmol/L compared to an increase of 2.2 mg/dL with placebo). Also, fewer patients receiving 25 mg alogliptin (15.7%) required hyperglycaemic rescue compared to those receiving placebo (28.3%) during the study. Body weight did not differ significantly between the groups.

Table 8. Glycemic Parameters at Week 26 for NESINA® When Added to a Sulfonylurea (Study SYR-322-007)

	NESINA® 25 mg	**Placebo**
$HbA1_c$ (%)	**N=198**	**N=99**
Baseline (mean)	8.09	8.15
Change from Baseline at Week 26†	-0.52 ± 0.058 (n=197)	0.01 ± 0.084 (n=97)
Difference vs. Placebo†	-0.53%* [-0.73, -0.33]	
Patients (%) achieving HbA1c ≤7% at Week 26	34.8	18.2
FPG (mmol/L)	**N=198**	**N=99**
Baseline (mean)	9.65	9.84
Change from Baseline at Week 26†	-0.47 ±0.19 (n=198)	0.12 ± 0.26 (n=99)
Difference vs. Placebo†	-0.58 mmol/L [-1.22, 0.05]	

†Least squares mean ± SE
* p<0.01, [ ] shows two-sided 95% confidence interval

Figure 4. Change from Baseline at Week 26 in HbA1c When NESINA® 25 mg is Added on to Sulfonylurea (SU)



Alogliptin as Add-on Therapy to Pioglitazone (PIO) (*SYR-322-TZD-009)*

The addition of 25 mg alogliptin once daily to pioglitazone therapy (mean dose = 35.0 mg, with or without metformin or a sulfonylurea) resulted in statistically significant improvements from baseline in HbA1c (see Figure 5) and FPG at Week 26 when compared to the addition of placebo (Table 9). Approximately 56% and 21% of subjects were receiving metformin or sulfonylurea at baseline. Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin or sulfonylurea therapy. Also, fewer patients receiving 25 mg alogliptin (9.0%) required hyperglycemic rescue compared to those receiving placebo (12.4%) during the study. Body weight did not differ significantly between the groups.

Table 9. Glycemic Parameters at Week 26 for NESINA® When Added to Pioglitazone (Study SYR-322_009)

	NESINA® 25 mg	**Placebo**
$HbA1_c$ (%)	**N=199**	**N=97**
Baseline (mean)	8.01	7.97
Change from Baseline at Week 26†	0.80 ± 0.056 (n=195)	-0.19 ± 0.081 (n=95)
Difference vs. Placebo†	-0.61% *	

	[-0.80, -0.41]	
Patients (%) achieving HbA1c ≤7% at Week 26	49.2	34.0
FPG (mmol/L)	**N=199**	**N=97**
Baseline (mean)	9.41	9.53
Change from Baseline at Week 26†	-1.10 ± 0.15 (n=197)	-0.32 ± 0.21 (n=97)
Difference vs. Placebo†	-0.78 mmol/L* [-1.29, -0.28]	

†Least squares mean ± SE
* p<0.01, [ ] shows two-sided 95% confidence interval

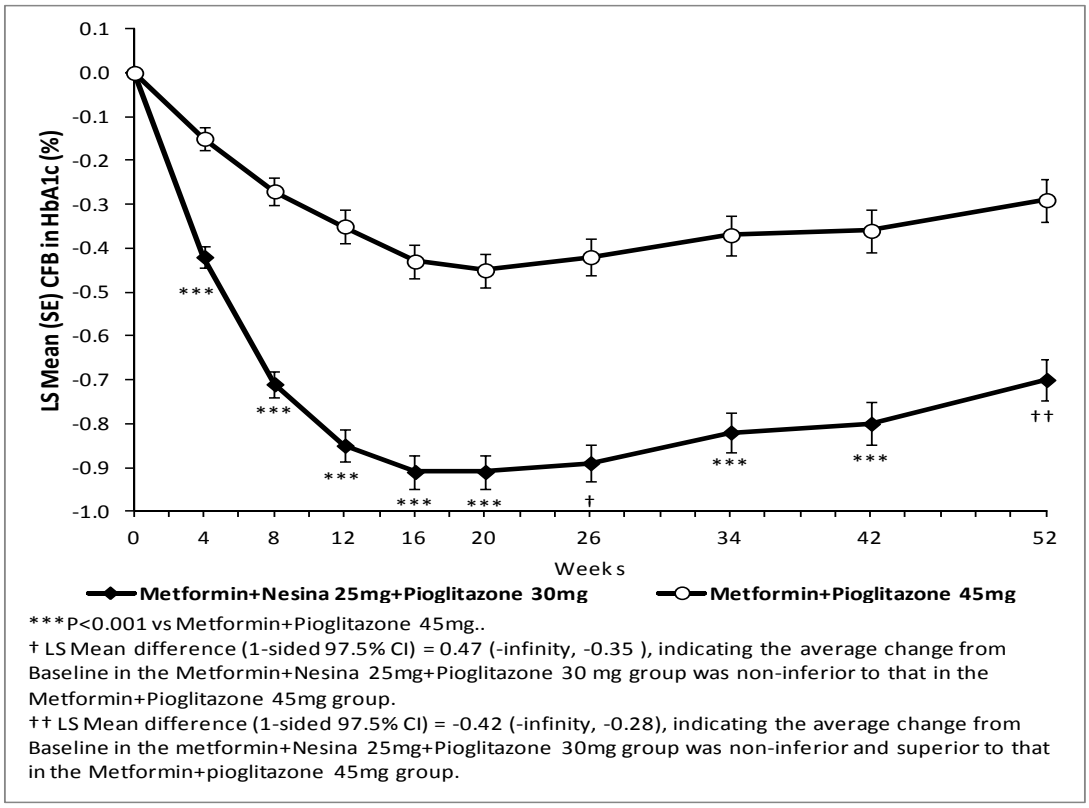
Alogliptin as Add-on Therapy to Pioglitazone with Metformin (01-06-TL-322OPI-004)
The addition of 25 mg alogliptin once daily to 30 mg pioglitazone and metformin therapy (mean dose = 1867.9 mg) resulted in clinically meaningful improvements from baseline in HbA1c at Week 52 (see Figure 5) that were both non-inferior and statistically superior to those produced by 45 mg pioglitazone and metformin therapy (mean dose = 1847.6 mg, Table 10). The significant reductions in HbA1c observed with 25 mg alogliptin plus 30 mg pioglitazone and metformin were consistent over the entire 52-week treatment period compared to 45 mg pioglitazone and metformin (p<0.001 at all time points). Also, fewer patients receiving 25 mg alogliptin plus 30 mg pioglitazone and metformin (10.9%) required hyperglycemic rescue compared to those receiving 45 mg pioglitazone and metformin (21.7%) during the study. Body weight did not differ significantly between the groups.

Table 10. Glycemic Parameters at Week 52 for NESINA® as Add-on Combination Therapy with Pioglitazone and Metformin (Study 322OPI-004)

	NESINA® 25 mg + Metformin hydrochloride (≥1500) + Pioglitazone 30 mg	**Metformin hydrochloride (≥1500) + Pioglitazone 45 mg**
$HbA1_c$ (%)	**N=404**	**N=399**
Baseline (mean)	8.24	8.14
Change from Baseline at Week 52 (Per protocol set)†	-0.70 ± 0.048 (n=303)	-0.29 ± 0.048 (n =306)
Difference vs. Metformin + Pioglitazone†	-0.42% [-infinity, -0.28]	
Patients (%) achieving HbA1c ≤7% at Week 52	33.2	21.3
FPG (mmol/L)	**N=404**	**N=399**
Baseline (mean)	8.98	9.00
Change from Baseline at Week 52 (Full Analysis Set) †	-0.81 ± 0.10 (n=399)	-0.21 + 0.10 (n=396)
Difference vs. Metformin + Pioglitazone†	-0.60 mmol/L* <-0.90, -0.32>	

†Least squares mean ± SE
*p<0.001, [ ] shows one-sided 97.5% confidence interval, < > shows two-sided 95% confidence interval

Figure 5. Change from Baseline at Week 26 in HbA1c When NESINA® 25 mg is Added on to Pioglitazone with Metformin



***P<0.001 vs Metformin+Pioglitazone 45mg..
† LS Mean difference (1-sided 97.5% CI) = 0.47 (-infinity, -0.35), indicating the average change from Baseline in the Metformin+Nesina 25mg+Pioglitazone 30 mg group was non-inferior to that in the Metformin+Pioglitazone 45mg group.
†† LS Mean difference (1-sided 97.5% CI) = -0.42 (-infinity, -0.28), indicating the average change from Baseline in the metformin+Nesina 25mg+Pioglitazone 30mg group was non-inferior and superior to that in the Metformin+pioglitazone 45mg group.

Alogliptin as Add-on Therapy to Insulin (With or Without Metformin) (SYR-322-INS-011)

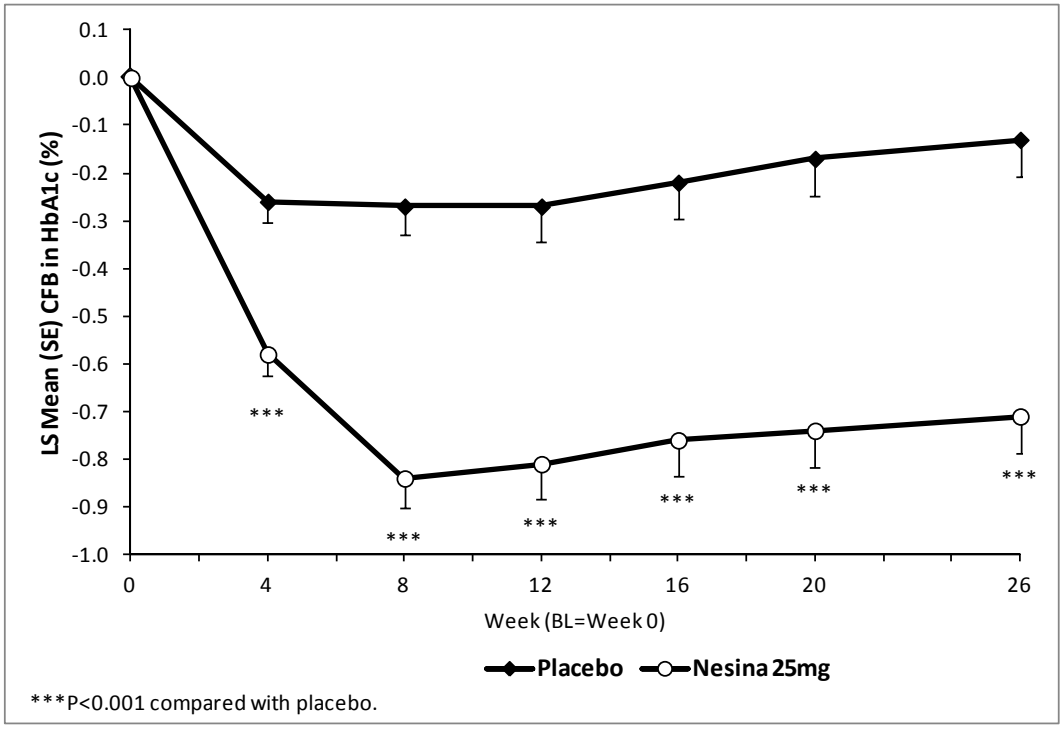
Alogliptin was investigated in patients with a baseline HbA1c ≥8.0 and taking insulin at doses ranging from 15 to 100 IU/day either as monotherapy (42% of the total sample) or in combination with insulin (58% of the total sample). The majority of insulins used in this study were mixed and basal classes. The addition of 25 mg alogliptin once daily to insulin therapy (mean dose = 56.5 IU, with or without metformin) resulted in statistically significant improvements from baseline in HbA1c (see Figure 6) and FPG at Week 26 when compared to the addition of placebo (Table 11). The completion rates in the study were low (42% completed in the placebo group and 60% completed in the alogliptin 25 mg group). Fewer patients receiving 25 mg alogliptin (19.4%) required hyperglycemic rescue compared to those receiving placebo (40%) during the study. Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin therapy. Significant improvements in HbA1c vs. placebo were noted as early as 4 weeks after the start of NESINA®, which remained significant at every time point until study end. Body weight did not differ significantly between the groups.

Table 11. Glycemic Parameters at Week 26 for NESINA® as Add-on Combination Therapy with Insulin (with or without Metformin) (Study 322-INS-011)

	NESINA® 25 mg	**Placebo**
$HbA1_c$ (%)	**N=129**	**N=129**
Baseline (mean)	9.27	9.28
Change from Baseline at Week 26†	-0.71 ± 0.078 (n=126)	-0.13 ± 0.077 (n=126)
Difference vs. Placebo†	-0.59% * [-0.80, -0.37]	
Patients (%) achieving HbA1c ≤7% at Week 26	7.8	0.8
FPG (mmol/L)	**N=129**	**N=129**
Baseline (mean)	10.34	10.88
Change from Baseline at Week 26†	-0.65 ± 0.32 (n=128)	0.32± 0.32 (n=127)
Difference vs. Placebo†	-0.98 mmol/L * [-1.85, -0.09]	

†Least squares mean ± SE
*p<0.05, [ ] shows two-sided 95% confidence interval

Figure 6. Change from Baseline at Week 26 in HbA1c When NESINA® 25 mg is Added to Insulin



Patients with Renal Impairment
The efficacy and safety of the recommended doses of alogliptin in a subgroup of patients with type 2 diabetes mellitus and mild and moderate renal impairment were reviewed and found to be consistent with the profile obtained in patients with normal renal function.

Geriatrics (≥65 years old)
Treatment with 25 mg alogliptin once daily resulted in improvements from baseline in HbA1c at Week 52 that were non-inferior (HbA1c change from baseline to Week 52 = -0.14%) to those produced by glipizide (HbA1c change from baseline to Week 52 = -0.09%; mean dose of glipizide = 5.4 mg).

Other Studies

Cardiovascular Safety

In a prospective, multicenter, randomized, double-blind, placebo-controlled cardiovascular outcomes safety study, treatment with NESINA® resulted in rates of major adverse cardiovascular events (MACE) that were comparable to those observed with placebo in addition to standard of care among patients with type 2 diabetes and a history of acute coronary syndrome within 15 to 90 days prior to randomization. Subjects were randomized in a 1:1 ratio to NESINA® or placebo. Randomization was stratified based on country and screening renal function (normal renal function/mild renal impairment vs moderate/severe renal impairment including ESRD). The assigned dose of NESINA® was based on renal function at screening:

- Subjects with normal renal function or mild renal impairment (eGFR ≥60 mL/min using the MDRD formula at Screening) received NESINA® 25 mg QD or matching placebo.
- Subjects with moderate renal impairment (eGFR ≥30 and <60 mL/min using the MDRD formula at Screening) received NESINA® 12.5 mg QD or matching placebo.
- Subjects with severe renal impairment/ESRD (eGFR <30 mL/min using the MDRD formula at Screening) received NESINA® 6.25 mg QD or matching placebo.

The cardiovascular outcomes safety study was conducted with 5,380 patients (67.9% male, 32.1% female) to examine the effect of alogliptin compared with placebo (when added to standard of care) on major adverse cardiovascular events (MACE) including time to the first occurrence of any event in the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. At baseline, patients had a mean age of 61 years, mean duration of diabetes of 9.2 years, and mean HbA1c of 8.0%. Cardiovascular history reported for patients in this study included: MI (88%), congestive heart failure (27.9%), unstable angina (31.1%), cerebrovascular accident (CVA) (7.2%), hypertension (83.1%), dyslipidemias (27.0%). Renal function category at baseline was categorized as normal in 15.6% of subjects, mild impairment in 55.3% of subjects, moderate impairment in 26.2% of subjects, and severe impairment/ESRD in 2.9% of subjects. Geographical distribution was 28.0% from Eastern Europe and Africa, 25.9% from Mexico and Central/South America, 18.8% from Asia/Pacific, 15.9% from United States and Canada, and 11.4% from Western Europe, Australia, New Zealand, and the Middle East.

The study demonstrated that alogliptin did not increase the risk of having a MACE compared to placebo [Hazard Ratio: 0.96; 1-sided 99% Confidence Interval: 0-1.16]. In the alogliptin group, 11.3% of patients experienced a MACE compared to 11.8% of patients in the placebo group (Table 12). For the analysis of each component of the primary MACE composite endpoint, time to first event was defined as the time from the date of randomization to the date of first occurrence of the component, only if it was counted in the primary MACE composite endpoint; otherwise, the subject was censored at the day of last contact.

Table 12. MACE Reported in Cardiovascular Outcomes Study

	Number of Patients (%)		
	Alogliptin	**Placebo**	**Hazard Ratio (1-sided 99% CI)**
	N=2701	N=2679	
Primary Composite Endpoint [First Event of CV Death, Nonfatal MI or Nonfatal Stroke]	**305 (11.3)**	**316 (11.8)**	0.96 (0 - 1.16)
Cardiovascular Death	89 (3.3)	111 (4.1)	
Nonfatal Myocardial Infarction	187 (6.9)	173 (6.5)	
Nonfatal Stroke	29 (1.1)	32 (1.2)	

There were 703 patients who experienced an event within the secondary MACE composite endpoint (first event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and urgent revascularization due to unstable angina). In the alogliptin group, 12.7% (344 subjects) experienced an event within the secondary MACE composite endpoint, compared with 13.4% (359 subjects) in the placebo group [Hazard Ratio = 0.95; 1-sided 99% Confidence Interval: 0-1.14].

Adjudicated events of total mortality, cardiovascular death, fatal/nonfatal myocardial infarction, fatal/nonfatal stroke, and heart failure resulting in death or hospitalization in all subjects (i.e., not excluding those events occurring after a non-fatal event included in a composite endpoint) had hazard ratios with 2-sided 95% confidence intervals including unity.

Table 13. Other Adjudicated Events Reported in All Subjects in Cardiovascular Outcomes Study

	Number of Patients (%)		Hazard Ratio (2-sided 95% CI)
	Alogliptin	**Placebo**	
	N=2701	N=2679	
All Cause Mortality	153 (5.7%)	173 (6.5%)	0.875 (0.705, 1.088)
Cardiovascular Death	112 (4.1%)	130 (4.9%)	0.851 (0.662, 1.096)
Myocardial Infarction: Fatal and Nonfatal	204 (7.6%)	190 (7.1%)	1.071 (0.878, 1.305)
Stroke: Fatal and Nonfatal	36 (1.3%)	44 (1.6%)	0.814 (0.524, 1.264)
Heart Failure: Hospitalization for Heart Failure and Death due to Heart Failure or Cardiogenic Shock	121 (4.5%)	99 (3.7%)	1.226 (0.940, 1.599)

DETAILED PHARMACOLOGY

Non-Clinical Pharmacodynamics

Alogliptin exists predominantly as the (*R*)-enantiomer (>99%) and undergoes little or no enantiomeric conversion to the (*S*)-enantiomer *in vivo*. Alogliptin is metabolized to 2 minor metabolites, an *N*-demethylated metabolite (M-I) and an *N*-acetylated metabolite (M-II). *In vitro*, alogliptin is a potent and highly selective inhibitor of DPP-4 activity. Alogliptin- mediated inhibitory activity was not observed against DPP2, DPP-8, DPP-9, PEP, FAP-α, PREP and tryptase. M-I has similar DPP-4 inhibitory activity as alogliptin and displays similar enzyme selectivity. The (*S*)-enantiomer exhibited minimal DPP-4 inhibitory activity (IC_{50} = 1045 nM), and M-II showed no inhibition at the highest concentration evaluated.

In vivo, oral administration of alogliptin to mice, rats, dogs, and monkeys inhibited the activity of plasma DPP-4. When administered to animal models of T2DM, alogliptin improved various disease indices including glucose tolerance, glycosylated hemoglobin, and plasma and pancreatic insulin content. Immunohistochemical analysis of pancreatic beta cells isolated from diabetic *ob/ob* mice administered alogliptin for 4 weeks revealed an increase in the intensity of insulin staining in these cells but with no obvious change in the number or size of beta cells. There were no changes in glucagon staining pancreatic alpha cells.

Non-Clinical Pharmacokinetics

Alogliptin was absorbed rapidly after oral administration with relatively high bioavailability across species (42% to 88%). After oral administration of [^{14}C]alogliptin to rats, a broad tissue distribution was evident, but drug-derived radioactivity did not readily cross the blood/brain

barrier. The metabolism of alogliptin was similar and limited in all species evaluated (rat, mouse, dog, monkey, and human). [^{14}C]Alogliptin was excreted rapidly in all species following oral administration. The major route of elimination was via feces, followed by urine.

Clinical Pharmacokinetics

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

In vivo
After administration of single, oral doses of up to 800 mg in healthy subjects, alogliptin was rapidly absorbed with peak plasma concentrations occurring 1 to 2 hours (median T_{max}) after dosing. Steady state concentrations are achieved with minimal accumulation in both healthy subjects (~1.4-fold accumulation) and in patients with type 2 diabetes mellitus (~1.3-fold accumulation). The inter-subject coefficient of variation for alogliptin AUC was small (17%).

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. Protein binding of alogliptin is approximately 20% and is similar in healthy subjects and subjects with renal impairment. Alogliptin does not undergo extensive metabolism as the majority of the dose is excreted as unchanged drug in the urine. Alogliptin is eliminated with a mean half-life of approximately 21 hours.

Clinical Pharmacodynamics
Single-dose administration of alogliptin 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 alogliptin (at doses of 25 to 200 mg) than placebo.

Administration of 25 mg alogliptin to patients with type 2 diabetes mellitus produced peak inhibition of DPP-4 within 1 to 2 hours and exceeded 93% both after a single 25 mg dose and after 14 days of once-daily dosing. Inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing. In clinical studies, postprandial active GLP-1 levels were consistently increasing compared to placebo and postprandial glucose concentrations were consistently reduced compared to placebo.

TOXICOLOGY

Acute Toxicity
Alogliptin was well tolerated by study animals. The single lethal oral dose of alogliptin in rats and dogs exceeded 1471 mg/kg and 368 mg/kg, respectively.

Chronic Toxicity

The toxicity potential of alogliptin was evaluated in a series of repeated dose toxicity studies in rats and dogs of up to 26 and 39 weeks in duration, respectively. In rats, the main target organs of toxicity of alogliptin were the liver, kidney and urinary bladder. Moderate liver toxicity was noted at doses of ≥900 mg/kg/day as reflected by elevated serum AST, ALT and/or ALP activities, increased liver weights, as well as minimal to mild centrilobular hepatocellular hypertrophy. At doses of ≥1333 mg/kg/day, in addition to the liver, toxicities on kidney and urinary bladder were evident. In the kidneys, renal tubular degeneration and/or regeneration and renal tubular dilatation and/or necrosis were observed. In the urinary bladder, transitional cell hyperplasia (simple or papillary/nodular), hemorrhage, and inflammation, erosion/ulceration, and dilatation were noted. The urinary bladder and/or kidney complications contributed in part to an increase in mortality in rats from 1333 to 2000 mg/kg/day. The no-observed-adverse-effect-level in rats was 400 mg/kg, approximately 147 times the exposure in humans at the maximum recommended human adult dose (MRHD) of 25 mg alogliptin. In dogs, reddened ears and facial swelling, without associated histopathological changes, were noted at doses of ≥30 mg/kg/day. The no-observed-adverse-effect-level in dogs derived from the 39-week study was 100 mg/kg/day, approximately 112 times the exposure in humans at the MRHD.

Carcinogenicity

A two-year carcinogenicity study was conducted in rats at oral doses of 75, 400 and 800 mg/kg/day alogliptin. No treatment-related tumors were observed in either male or female rats given 75 mg/kg/day alogliptin (approximately 27 times human exposure at the MRHD). Increases in the combined incidence of C-cell adenoma and/or carcinoma were only observed in male rats at doses of ≥400 mg/kg/day (≥245 times human exposure at the MRHD). Increases in non-neoplastic histopathological changes in the liver, lung, urinary bladder, testes, epididymis, and prostate were noted in rats at doses that were at least 240 times the exposure in humans at the MRHD.

A two-year carcinogenicity study was conducted in mice at oral doses of 50, 150 and 300 mg/kg/day alogliptin. No treatment-related tumors were observed in either male or female mice at doses up to 300 mg/kg/day, approximately 51 times the exposure in humans at the MRHD.

Mutagenesis

Alogliptin was negative in a battery of genetic toxicology studies, including the Ames bacterial assay (microbial mutagenesis test), an *in vitro* cytogenetic assay in mouse lymphoma cells, and an *in vivo* mouse micronucleus study.

Reproduction

No adverse effects of alogliptin were observed upon fertility, reproductive performance, or early embryonic development in rats given alogliptin orally at doses up to 500 mg/kg/day (up to approximately 191 times human exposure at the MRHD) prior to and throughout mating. Although fertility was not affected, a slight increase in the percent of abnormal sperm was noted at 1000 mg/kg/day (approximately 392 times human exposure at the MRHD).

Development
Placental transfer of alogliptin occurs in rats following oral dosing.

Alogliptin was not teratogenic in rabbits and rats at oral doses up to 200 and 500 mg/kg/day (up to approximately 149 and 180 times human exposure at the MRHD) given during organogenesis, respectively. Higher doses of alogliptin resulted in maternal toxicity, and were associated with delayed and/or lack of ossification of bones and decreased fetal body weights. The non-observed-adverse-effect-level for embryo-fetal development in rabbits and rats was 200 mg/kg/day and 500 mg/kg/day (approximately 149 and 180 times human exposure at the MRHD), respectively.

Alogliptin at oral doses up to 250 mg/kg/day (up to approximately 95 times human exposure at the MRHD) given to pregnant rats from gestation day 6 to lactation day 20 did not harm the developing embryo or affect offspring growth and development. Higher doses of alogliptin, providing exposures exceeding 200 times the exposure in humans at the MRHD, decreased F1 offspring body weights and induced some developmental effects.

No alogliptin-related effects were observed in juvenile rats following repeated oral dosing for 4 and 8 weeks at doses up to 300 mg/kg/day (up to approximately 63 and 75 times human exposure at the MRHD, respectively).

Safety Pharmacology
The cardiovascular safety of alogliptin was evaluated. Alogliptin was not observed to inhibit hERG channel tail currents in stably transfected HEK-293 and CHO cells, and exhibited no effect on action potential parameters in isolated canine cardiac Purkinje fibres. In conscious telemetered beagle dogs, cardiovascular function was assessed following administration of single oral doses of 0, 7.5, 15, and 25 mg/kg alogliptin. No effects on heart rate, blood pressure, cardiac troponin levels (I and T isoforms) or ECG interval parameters were observed.

Respiratory safety was evaluated in rats following a single oral dose 0, 10, 30 and 100 mg/kg alogliptin. There were no alterations in respiratory rate, minute volume or tidal volume.

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PART III: CONSUMER INFORMATION

PrNESINA®
alogliptin (as alogliptin benzoate)

This leaflet is part III of a three-part "Product Monograph" published when NESINA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NESINA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
NESINA® can be used to improve blood sugar levels in adult patients with type 2 diabetes in addition to diet and exercise:

- alone in patients who cannot take metformin
- in combination with metformin
- in combination with a sulfonylurea
- in combination with pioglitazone
- in combination with insulin (with or without metformin)
- in combination with pioglitazone and metformin

What it does:
NESINA® is used when your blood sugar cannot be adequately controlled by diet, exercise and one or more of these other oral antidiabetic medicines. It is important that you continue to take your other antidiabetic medication, and continue to follow the advice on diet and exercise that your nurse or doctor has given you.

When it should not be used:
You should not take NESINA® if you:

- are allergic to alogliptin or any of the other ingredients of this medicine
- are pregnant or planning to become pregnant
- are breast-feeding

What the medicinal ingredient is:
Alogliptin benzoate

What the nonmedicinal ingredients are:
mannitol, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, hypromellose 2910, titanium dioxide (E171), red iron oxide (E172) (present in 25 mg and 6.25 mg tablets), yellow iron oxide (E172) (present in 12.5mg tablets), polyethylene glycol (Macrogol 8000), printing ink (Gray F1).

What dosage forms it comes in:
Tablets, 6.25 mg, 12.5 mg, and 25 mg

WARNINGS AND PRECAUTIONS

Before you take NESINA®, tell your doctor if you:

- have type 1 diabetes (your body does not produce insulin)
- have diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to breakdown glucose because there is not enough insulin). Symptoms include excessive thirst, frequent urination, loss of appetite, nausea or vomiting and rapid weight loss
- are taking the anti-diabetic medicines pioglitazone and metformin or a medicine known as sulfonylurea (e.g. glipizide, tolbutamide, glibenclamide) or insulin (with or without metformin). Your doctor may want to reduce your dose of sulfonylurea or insulin when you take any of them together with NESINA® in order to avoid too low blood sugar. Take precaution to avoid low blood sugar while driving or using machinery.
- have or have had kidney disease
- suffer from heart failure
- have or have had liver problems
- have any allergies, especially to the ingredients in NESINA®
- have or have had an inflammation of your pancreas (pancreatitis)
- have had allergic reactions to any other medications that you take to control your blood sugar. Symptoms may include general itching and feeling of heat especially affecting the scalp, mouth, throat, palms of hands and soles of feet, as well as blistering (Stevens-Johnson Syndrome)

INTERACTIONS WITH THIS MEDICATION

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

Talk to your doctor before starting any new medicine.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose of NESINA® is 25 mg once a day. Swallow your tablet(s) whole with water. You can take this medicine with or without food.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor may prescribe NESINA® together with another medicine to control your blood sugar levels.

Your doctor will tell you if you need to change the amount of other medicines you take.

If you have kidney disease your doctor may prescribe you a reduced dose.

Overdose:
If you take more tablets than you should, or if someone else or a

child takes your medicine, contact or go to your nearest emergency centre straight away. Take this leaflet or some tablets with you so that your doctor knows exactly what you have taken.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose. Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, NESINA® may cause unwanted reactions, known as side effects. Tell your doctor if you have any of the following side effects:

- cold or flu like symptoms such as sore throat, stuffy or blocked nose, feeling tired, fever, chills, body ache, dry cough
- rash or itchy skin
- headache
- abdominal pain
- stomach pain
- nausea
- toothache
- vomiting
- constipation
- indigestion, heartburn
- back pain
- muscle and/or bone pain (including of the chest)
- cramp
- tiredness (fatigue)
- difficulty sleeping
- tiredness, weakness, dizziness or pale complexion due to low red blood cells (anaemia)
- swelling of extremities
- high cholesterol or fat in blood
- joint pain
- pain, numbness or sensation of “pins and needles” in extremities
- high blood pressure (hypertension)

NESINA® can cause abnormal blood test results. Your doctor will decide when to perform tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Low blood sugar (hypoglycemia): (when used with metformin and pioglitazone, or with a sulfonylurea, or when used with insulin with or without metformin) trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change or feeling confused			√
Uncommon	Allergic reaction: severe rash, hives, swallowing or breathing problems, swelling of your lips, face, throat, tongue and feeling faint			√
Uncommon	Pancreatitis (inflamed pancreas): Severe and persistent pain around the top of stomach which may reach to your back, with or without vomiting		√	√
Very Rare	Bullous pemphigoid (serious skin reaction): blistering of the skin, redness or peeling skin		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	Stevens-Johnson syndrome (a severe allergic reaction): serious rash, skin reddening, pain, swelling of lips, eyes or mouth, skin peeling and flu-like symptoms			√
Very Rare	Liver disorders: nausea or vomiting, stomach pain, unusual or unexplained tiredness, loss of appetite, dark urine or yellowing of your skin or the whites of your eyes.		√	√

This is not a complete list of side effects. For any unexpected effects while taking NESINA®, contact your doctor or pharmacist.

HOW TO STORE IT

Store NESINA® at 15 – 30° C.

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

NESINA® does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.takedacanada.com/
or by contacting the sponsor, Takeda Canada Inc. at:
1-866-295-4636.

This leaflet was prepared by Takeda Canada Inc., Oakville, Ontario L6H 0J8

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