AUSTRALIAN PRODUCT INFORMATION

NESINA® (ALOGLIPTIN BENZOATE)

1 NAME OF THE MEDICINE

Alogliptin benzoate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NESINA is available for oral use as film-coated tablets containing alogliptin benzoate equivalent to 6.25, 12.5 or 25 mg of free base.

Contains benzoates.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

NESINA is available in the following presentations:

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

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

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NESINA is indicated to improve glycaemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control, as add on to metformin, a sulphonylurea, a thiazolidinedione, insulin (with or without metformin), or in combination with metformin and a thiazolidinedione when dual therapy does not provide adequate glycaemic control.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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

Adults (≥ 18 years old)

The recommended dose of NESINA is 25 mg once daily. NESINA is not indicated for initial combination therapy.

When NESINA is used in combination with metformin and/or a thiazolidinedione, the dose of metformin and/or the thiazolidinedione should be maintained, and NESINA administered concomitantly.

When NESINA is used in combination with insulin or an insulin secretagogue such as a sulfonylurea, a lower dose of insulin or insulin secretagogue may be considered to minimise the risk of hypoglycaemia. The combination of insulin and alogliptin has not been specifically studied in T2DM patients with moderate or severe renal failure. Caution is therefore required regarding risk of hypoglycaemia in this circumstance.

The safety and efficacy of NESINA when used as triple therapy with metformin and a sulphonylurea have not been fully established.

Special populations

Hepatic impairment

No dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Grade A and B or scores of 5 to 9). NESINA has not been studied in patients with severe hepatic impairment (Child-Pugh Grade C or score > 9) and is, therefore, not recommended for use in such patients.

Renal impairment

For patients with mild renal impairment (creatinine clearance >50 to ≤80 mL/min), no dose adjustment of NESINA is necessary.

For patients with moderate renal impairment (creatinine clearance ≥30 to ≤50 mL/min), the recommended dose of NESINA is 12.5 mg once daily.

For patients with severe renal impairment (creatinine clearance <30 mL/min) or End-Stage Renal Disease (ESRD) requiring dialysis, the recommended dose of NESINA is 6.25 mg once daily. NESINA may be administered without regard to the timing of dialysis. Experience in patients requiring renal dialysis is limited. Alogliptin has not been studied in patients undergoing peritoneal dialysis (see Section 5.2 Pharmacokinetic Properties, Special Populations, Renal Impairment).

Appropriate assessment of renal function is recommended prior to initiation of NESINA and periodically thereafter.

Elderly (≥ 65 years old)

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 (see also Section 4.2 Dose and Method of Administration, Renal Impairment).

Paediatric population

The safety and efficacy of NESINA in patients under 18 years of age have not yet been established.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients [see Section 4.8 Adverse Effects (Undesirable Effects)].

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

Use with other antihyperglycaemic medications and hypoglycaemia

Clinical trials of NESINA alone or as add-on therapy to metformin or a thiazolidinedione demonstrated that there was no clinically relevant increase in hypoglycaemia rate compared to placebo. In a clinical trial of NESINA as add-on therapy to a sulphonylurea, the incidence of hypoglycaemia was lower than that of placebo. The incidence of hypoglycaemia was greater in studies of NESINA as add-on therapy to metformin with a thiazolidinedione and as add-on therapy to insulin (with or without metformin) compared to active-control or placebo, respectively [see Section 4.8 Adverse Effects (Undesirable Effects)].

Insulin and insulin secretagogues, such as sulphonylureas, are known to cause hypoglycaemia. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimise the risk of hypoglycaemia when used in combination with alogliptin (see Section 4.2 Dose and Method of Administration).

Cardiac failure

There is limited experience of alogliptin use in clinical trials in patients with congestive heart failure of New York Heart Association (NYHA) functional class IV. NESINA should, therefore, be used with caution in these patients [see Section 4.8 Adverse Effects (Undesirable Effects)].

Hypersensitivity Reactions

Postmarketing events of serious hypersensitivity reactions in patients treated with alogliptin such as angioedema and severe cutaneous adverse reactions including Stevens-Johnson syndrome have been reported and have been associated with other DPP-4 inhibitors. If a serious hypersensitivity reaction is suspected, alogliptin should be discontinued.

Acute Pancreatitis

Postmarketing events of acute pancreatitis have been reported for alogliptin and have been associated with other DPP-4 inhibitors. After initiation of alogliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, alogliptin should be promptly discontinued and appropriate management should be initiated.

Hepatic effects

Postmarketing reports of hepatic dysfunction including hepatic failure have been received. Patients should be observed closely for possible liver abnormalities. Obtain liver function tests promptly in patients who report symptoms that may indicate liver injury. If an abnormality is found and an alternative etiology is not established, consider discontinuation of alogliptin treatment.

Arthralgia

There have been post-marketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with alogliptin.

Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic

immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to 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.

Use in hepatic impairment

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 Sections 5.2 Pharmacokinetic Properties and Section 4.2 Dose and Method of Administration).

Use in renal impairment

As there is a need for dose adjustment in patients with moderate or severe renal impairment, or End Stage Renal Disease (ESRD) requiring dialysis, appropriate assessment of renal function is recommended prior to initiation of NESINA and periodically thereafter (see Section 4.2 Dose and Method of Administration).

Experience in patients requiring renal dialysis is limited. Alogliptin has not been studied in patients undergoing peritoneal dialysis (see Sections 5.2 Pharmacokinetic Properties and Section 4.2 Dose and Method of Administration).

Use in the elderly

No dose adjustment of NESINA is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function in this population (see Section 4.4 Special Warnings and Precautions for Use, Use in Renal Impairment).

Paediatric use

The safety and efficacy of NESINA in patients < 18 years old have not yet been established. No data are available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

NESINA is primarily renally excreted and CYP-related metabolism is negligible. No drug-drug interactions were observed with the CYP-substrates or inhibitors tested, or with renally excreted drugs.

***In Vitro* Assessment of Drug Interactions**

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

In *in vitro* studies, alogliptin was found to be neither a substrate nor an inhibitor of key transporters associated with drug disposition in the kidney: organic anion transporter-1 (OAT1), organic anion transporter-3 (OAT3) or organic cationic transporter-2 (OCT2). However, renal clearance of alogliptin (approximately 170 mL/min) exceeds GFR (120 mL/min), indicating net renal active excretion by an unknown mechanism.

In Vivo Assessment of Drug Interactions

Effects of Alogliptin on Other Drugs

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

Digoxin: Administration of NESINA 25 mg once daily with a P-glycoprotein substrate, digoxin 0.2 mg, once daily for 10 days had no meaningful effect on the pharmacokinetics or the renal clearance of digoxin.

Warfarin: Administration of NESINA 25 mg once daily with stable doses of warfarin once daily for 7 days had no meaningful effect on the pharmacokinetics of (S)-warfarin (a CYP2C9 substrate) and (R)-warfarin (a CYP1A2 substrate). In healthy subjects, alogliptin had no effect on prothrombin time (PT) or International Normalized Ratio (INR).

Metformin: Administration of alogliptin 100 mg once daily with metformin 1000 mg twice daily for 6 days had no meaningful effect on the pharmacokinetics and renal clearance of metformin.

Cimetidine: Administration of alogliptin 100 mg once daily with cimetidine 400 mg once daily for 6 days had no meaningful effect on the pharmacokinetics and renal clearance of cimetidine.

Sulfonylureas: Administration of NESINA 25 mg once daily for 8 days had no meaningful effect on the pharmacokinetics of a single dose of glibenclamide 5 mg.

Pioglitazone: Administration of NESINA 25 mg once daily with a CYP2C8 substrate, pioglitazone 45 mg, once daily for 12 days had no meaningful effect on the pharmacokinetics of pioglitazone and its active metabolites.

Atorvastatin: Administration of NESINA 25 mg once daily with a CYP3A4 substrate, atorvastatin 80 mg, once daily for 7 days had no meaningful effect on the pharmacokinetics of atorvastatin and its active metabolites.

Oral contraceptives: Administration of NESINA 25 mg once daily with an oral contraceptive (1 mg norethindrone and 35 mcg of ethinyl estradiol) for 21 days had no meaningful effect on the pharmacokinetics and pharmacodynamics of CYP3A4 substrates, norethindrone, and ethinyl estradiol.

Effects of Other Drugs on Alogliptin

Clinical data described below suggest that alogliptin is not susceptible to interactions when administered concomitantly with the drugs described below.

Ciclosporine: Administration of a single dose of a P-glycoprotein inhibitor, ciclosporine 600 mg, with a single dose of NESINA 25 mg did not result in any meaningful changes in the renal clearance of or systemic exposure to alogliptin. Interactions with other P-glycoprotein inhibitors are therefore not expected.

Voglibose: Co-administration of voglibose (an alpha-glucosidase inhibitor) and alogliptin did not result in any meaningful changes in the pharmacokinetics of alogliptin.

No significant increases in the single-dose systemic exposure to alogliptin were seen when administered concomitantly with multiple doses of drugs that inhibit CYP isozymes: fluconazole (CYP2C9 inhibitor), ketoconazole (CYP3A4 inhibitor), and gemfibrozil (CYP2C8 inhibitor). Since

alogliptin is primarily renally excreted and CYP-related metabolism is negligible, inhibitors of CYP enzymes are unlikely to affect exposure to alogliptin.

Results from clinical studies also demonstrate that there are no meaningful effects of digoxin, metformin, cimetidine, pioglitazone, or atorvastatin on the pharmacokinetics of alogliptin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of alogliptin on fertility in humans has not been studied.

No adverse effects of alogliptin were observed on fertility, reproductive performance, or early embryonic development in male and female rats given alogliptin orally at doses up to 500 mg/kg/day. The exposure margin at the NOAEL in rats was at least 170-fold the exposure in humans at the recommended dose of 25 mg alogliptin.

Use in pregnancy (Category B3)

There are no data from the use of alogliptin in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. As with other oral antihyperglycaemic agents, as a precautionary measure it is preferable to avoid the use of NESINA during pregnancy.

Placental transfer of alogliptin occurs in rats. Alogliptin was not teratogenic in rats or rabbits. The exposure margins at the NOAEL established in rats (500 mg/kg/day) and rabbits (200 mg/Kg/day) were approximately 180- and 149-fold, respectively, the exposure in humans at the recommended dose of 25 mg alogliptin. Higher doses of alogliptin were not teratogenic but resulted in maternal toxicity, and were associated with delayed and/or lack of ossification of bones and decreased fetal body weights.

In a pre- and postnatal development study in rats, doses of 250 mg/kg/day (approximately 95-fold the exposure in humans at the recommended dose of 25 mg alogliptin) did not harm the developing embryo or affect offspring growth and development. Higher doses of alogliptin, providing exposures exceeding 190 fold the human exposure, decreased offspring body weight without adversely affecting developmental behaviour, maturation and reproductive success.

Use in lactation

It is unknown whether alogliptin is excreted in human milk. Studies in lactating rats indicate that alogliptin is excreted in milk. A risk to the breastfeeding child cannot be excluded.

A decision on whether to discontinue breastfeeding or to discontinue NESINA therapy should be made taking into account the benefit of breastfeeding for the child and the benefit of NESINA therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

The information provided is based on a total of 9405 patients with type 2 diabetes mellitus, including 3750 patients treated with NESINA 25 mg and 2476 patients treated with NESINA 12.5 mg, who 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 patients randomised to alogliptin and 2679 patients randomised to placebo. These studies evaluated the effects of NESINA on glycaemic control and its safety as monotherapy, as initial combination therapy with metformin or a thiazolidinedione, and as add-on therapy to metformin, or a sulphonylurea, or a thiazolidinedione (with or without metformin or a sulphonylurea), or insulin (with or without metformin).

In a pooled analysis of the data from 13 studies, the overall incidences of adverse events, serious adverse events and adverse events resulting in discontinuation of therapy were comparable in patients treated with NESINA 25 mg, NESINA 12.5 mg, active control or placebo. The most common adverse reaction in patients treated with NESINA 25 mg was headache.

The safety of alogliptin between the elderly (≥ 65 years old) and non-elderly (< 65 years old) was similar.

Tabulated list of adverse reactions

In the pooled pivotal phase 3 controlled clinical trials of alogliptin as monotherapy and as add-on combination therapy involving 5659 patients, the observed adverse reactions are listed below (Table 1).

The adverse reactions are listed by system organ class and frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 1 Adverse reactions observed in pooled pivotal phase 3 controlled clinical studies

System Organ Class Adverse reaction	**Frequency of adverse reactions**
Infections and infestations	
Upper respiratory tract infection	Common
Nasopharyngitis	Common
Nervous system disorders	
Headache	Common
Gastrointestinal disorders	
Abdominal pain	Common
Gastroesophageal reflux disease	Common
Skin and subcutaneous tissue disorders	
Pruritus	Common
Rash	Common

Post-marketing experience

The following adverse events have been reported (frequencies not known; cannot be estimated from the available data): hypersensitivity reactions including anaphylaxis, angioedema, and severe cutaneous adverse reactions including Stevens-Johnson syndrome and bullous pemphigoid (see Section 4.4 Special Warnings and Precautions for Use); acute pancreatitis; hepatic dysfunction including hepatic failure; tubulointerstitial nephritis (TIN).

Description of selected adverse reactions

Hypoglycaemia

In a pooled analysis of the data from 12 studies, the overall incidence of any episode of hypoglycaemia was lower in patients treated with NESINA 25 mg than in patients treated with NESINA 12.5 mg, active control or placebo (3.6%, 4.6%, 12.9% and 6.2%, respectively). The majority of these episodes were mild to moderate in intensity. The overall incidence of episodes of severe hypoglycaemia was comparable in patients treated with NESINA 25 mg or NESINA 12.5 mg, and lower than the incidence in patients treated with active control or placebo (0.1%, 0.1%, 0.4% and 0.4%, respectively). In the prospective randomized controlled cardiovascular outcomes study,

investigator reported events of hypoglycaemia were similar in patients receiving placebo (6.5%) and patients receiving alogliptin (6.7%) in addition to standard of care. Therefore, based on this analysis, NESINA was considered to be risk neutral with respect to hypoglycaemia (see Section 4.4 Special Warnings and Precautions for Use).

Elderly patients (≥ 65 years old) with type 2 diabetes mellitus are considered more susceptible to episodes of hypoglycaemia than patients < 65 years old. In a pooled analysis of the data from 12 studies, the overall incidence of any episode of hypoglycaemia was similar in patients ≥ 65 years old treated with NESINA 25 mg (3.8%) to that in patients < 65 years old (3.6%).

Pancreatitis

In a pooled analysis of the data from 13 studies, the overall rates of pancreatitis reports in patients treated with NESINA 25 mg, NESINA 12.5 mg, active control or placebo were 2, 1, 1 or 0 events per 1000 patient years, respectively. In the cardiovascular outcomes study the rates of pancreatitis reports in patients treated with alogliptin or placebo were 3 or 2 events per 1000 patient years, respectively. Published epidemiological data have shown that patients with type 2 diabetes mellitus have an increased incidence of acute pancreatitis (0.54 to 4.22 per 1000 patient years) compared to patients without type 2 diabetes mellitus (0.3 to 1.49 per 1000 patient-years).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No adverse events associated with overdose of NESINA were reported during clinical development.

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 subjects with type 2 diabetes mellitus (equivalent to 32 times and 16 times the recommended daily dose of NESINA 25 mg, respectively). No serious adverse events were observed at these dose levels.

Treatment

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

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Alogliptin is a potent (IC50 around 7nM) and highly selective (>10,000 fold selectivity versus DPP-8 or DPP-9), reversible, competitive inhibitor of DPP-4, an enzyme that rapidly degrades incretin hormones.

The incretins are part of an endogenous hormonal system involved in the physiological regulation of glucose and insulin homeostasis. The incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released from the intestine throughout the day and their levels are markedly increased in response to ingestion of a meal. The incretins stimulate insulin synthesis and glucose-dependent insulin secretion by pancreatic beta-cells. This incretin effect accounts for approximately 70% of insulin secretion in response to a meal. GLP-1 also suppresses glucagon secretion from pancreatic alpha-cells which leads to reduced hepatic glucose production, delayed gastric emptying and increased satiety. In nonclinical models, GLP-1 and GIP have also been shown to preserve beta-cell mass through regulation of beta-cell neogenesis, proliferation and apoptosis.

In patients with type 2 diabetes mellitus, levels of GLP-1 are reduced and the actions of both GLP 1 and GIP are blunted. This markedly diminished incretin effect contributes to hyperglycaemia. DPP 4 inhibition targets the diminished incretin effect by increasing circulating blood levels of endogenous incretins which in turn increase insulin levels and decrease glucagon levels in a glucose-dependent manner. The increase in insulin levels enhances glucose uptake by tissues and the decrease in glucagon levels reduces hepatic glucose production leading to improved glycaemic control.

Alogliptin is selective for DPP-4 and 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 more than 10,000-fold more selective for DPP 4 than other related enzymes including DPP-8 and DPP-9.

Administration of NESINA 25 mg 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, 14 days of treatment with NESINA 25 mg resulted in a mean placebo-corrected reduction from baseline of 1.95 mmol/L.

Both NESINA 25 mg alone and in combination with 30 mg pioglitazone demonstrated significant decreases in postprandial glucose and postprandial glucagon whilst significantly increasing postprandial active GLP-1 levels at Week 16 compared to placebo ($p<0.05$). In addition, NESINA 25 mg alone and in combination with 30 mg pioglitazone produced statistically significant ($p<0.001$) reductions in total triglycerides at Week 16 as measured by postprandial incremental AUC(0 8) change from baseline compared to placebo.

<u>Cardiac Electrophysiology</u>

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

Clinical trials

NESINA has been studied as monotherapy, as initial combination therapy with metformin or a thiazolidinedione, and as add-on therapy to metformin, or a sulphonylurea, or a thiazolidinedione (with or without metformin or a sulphonylurea), or insulin (with or without metformin).

A total of 14779 patients with type 2 diabetes mellitus, including 6448 patients treated with NESINA 25 mg and 2476 patients treated with NESINA 12.5 mg, 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 NESINA on glycaemic control and its safety. In these studies, 2257 NESINA-treated patients were ≥ 65 years old and 386 NESINA-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/end-stage renal disease treated with NESINA.

Overall, treatment with the recommended daily dose of NESINA 25 mg improved glycaemic 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 haemoglobin (HbA1c) and fasting plasma glucose (FPG) compared to control from baseline to study endpoint. Reductions in HbA1c were similar across different subgroups including renal impairment, age, gender, race and body mass index (BMI). Clinically meaningful reductions in HbA1c compared to control were also observed with NESINA 25 mg regardless of baseline background medication dose. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Generally, the effects of NESINA on body weight and lipids were neutral.

<u>NESINA as add-on therapy to metformin</u>

The addition of NESINA 25 mg once daily to metformin therapy (mean dose = 1846.7 mg) resulted in statistically significant improvements from baseline in HbA1c and FPG at Week 26 when compared to the addition of placebo (Table 2) (Study SYR-322-MET-008). Significantly more patients receiving NESINA 25 mg (44.4%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (18.3%) at Week 26 ($p<0.001$). Also, significantly fewer patients receiving NESINA 25 mg (8.2%) required hyperglycaemic rescue compared to those receiving placebo (24.0%) during the study ($p=0.003$).

Improvements in HbA1c were not affected by gender, age, race, baseline BMI, or baseline metformin dose. Patients who entered the study with a higher baseline HbA1c level generally achieved a greater treatment effect. An analysis by baseline HbA1c demonstrated that patients who entered the study with HbA1c ≥ 8% and HbA1c ≥ 9% achieved significant mean reductions from baseline of -0.8% and -1.2% on NESINA 25 mg versus -0.3% and 0.5% on placebo at Week 26, respectively. A similar decrease in body weight was observed for both NESINA and placebo when given in combination with metformin at Week 26. Lipid effects were generally neutral.

In a second study (Study SYR-322-305) evaluating the addition of NESINA 25 mg versus glipizide to metformin therapy, the addition of NESINA 25 mg once daily to metformin therapy (mean dose = 1835.3 mg) resulted in improvements from baseline in HbA1c at Week 52 and week 104.

At Week 52, the HbA1c reduction by 25 mg alogliptin plus metformin (-0.61%, Table 3) was similar to that produced by glipizide (mean dose = 5.2 mg) plus metformin hydrochloride therapy (mean dose = 1,824 mg, -0.52%). At Week 104, the HbA1c reduction by 25 mg alogliptin plus metformin (-0.72%, Table 3) was significantly greater than that produced by glipizide plus metformin (-0.59%, $p<0.05$). Mean change from baseline in fasting plasma glucose for 25 mg alogliptin and metformin (-3.2 mg/dL) was significantly greater than that for glipizide and metformin (5.4 mg/dL, $p<0.001$). Significantly more patients receiving 25 mg alogliptin and metformin (48,5%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving glipizide and metformin (42.8%)

(p=0.004). A total of 23.2% of patients receiving NESINA 25 mg with metformin and 27.4% of patients receiving glipizide with metformin required glycaemic rescue. Although no formal statistical testing was conducted, there was no effect in HbA1c in relation to gender, age, race or baseline BMI.

Alogliptin was associated with a much lower rate of hypoglycaemia (10 times less) when compared with glipizide at Week 104. Patients treated with NESINA exhibited a significant mean decrease from baseline in body weight compared to a weight gain in patients administered glipizide (-0.89 kg vs. 0.95 kg). For total cholesterol, LDL, and triglycerides, changes from Baseline to Week 104 were statistically significantly better in the metformin + NESINA 25mg treatment group compared with the metformin + glipizide treatment group ($p \leq 0.05$).

NESINA as add-on therapy to a sulphonylurea (SU) (Study SYR-322-SULF-007)

The addition of NESINA 25 mg once daily to glibenclamide therapy (mean dose = 12.2 mg) resulted in statistically significant improvements from baseline in HbA1c at Week 26 when compared to the addition of placebo (Table 2). Mean change from baseline in FPG at Week 26 for NESINA 25 mg showed a reduction of 0.47 mmol/L compared to an increase of 0.12 mmol/L with placebo. Significantly more patients receiving NESINA 25 mg (34.8%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (18.2%) at Week 26 (p=0.002). Also, significantly fewer patients receiving NESINA 25 mg (15.7%) required hyperglycaemic rescue compared to those receiving placebo (28.3%) during the study (p=0.030).

Improvements in HbA1c were not affected by gender, age, race, baseline BMI, or baseline glibenclamide dose. Patients who entered the study with a higher baseline HbA1c level generally achieved a greater treatment effect. An analysis by baseline HbA1c demonstrated that patients who entered the study with a HbA1c ≥ 8% achieved a significant mean reduction from baseline of -0.7% on NESINA 25 mg versus -0.1% on placebo at Week 26. Body weight increased with NESINA 25 mg compared with placebo when given in combination with glibenclamide at Week 26. Lipid effects were generally neutral.

NESINA as initial combination therapy with a thiazolidinedione (TZD) (Study 01-06-TL-322OPI-002)

Co-administration of NESINA 25 mg and 30 mg pioglitazone once daily resulted in statistically significant improvements from baseline in HbA1c and FPG at Week 26 when compared to either NESINA 25 mg alone or 30 mg pioglitazone alone (Table 2). Significantly more patients receiving NESINA 25 mg and 30 mg pioglitazone (62.8%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving either NESINA 25 mg alone (24.4%, p<0.001) or 30 mg pioglitazone alone (33.7%, p<0.001) at Week 26. Also, fewer patients receiving NESINA 25 mg and 30 mg pioglitazone (2.5%) required hyperglycaemic rescue compared to those receiving either NESINA 25 mg alone (11.3%, p=0.018) or 30 mg pioglitazone alone (6.4%) during the study.

Improvements in HbA1c were not affected by gender, age, race or baseline BMI. Patients who entered the study with a higher baseline HbA1c level generally achieved a greater treatment effect. An analysis by baseline HbA1c demonstrated that patients who entered the study with a HbA1c ≥ 9% achieved a significant adjusted mean reduction in HbA1c from baseline of -2.3% on NESINA 25 mg co-administered with pioglitazone 30 mg versus -1.2% on NESINA 25 mg and -1.4% on pioglitazone 30 mg at Week 26. Body weight decreased with NESINA 25 mg alone, however body weight increases were observed with pioglitazone alone and NESINA co-administered with pioglitazone. NESINA co-administered with pioglitazone resulted in statistically significant increases in fasting HDL cholesterol and decreases in triglycerides when compared with NESINA alone, however these differences were not seen in comparison to pioglitazone alone. Changes in LDL and total cholesterol were similar between treatment groups.

NESINA as add-on therapy to a thiazolidinedione (TZD) (Study SYR-322-TZD-009)

The addition of NESINA 25 mg once daily to pioglitazone therapy (mean dose = 35.0 mg, with or without metformin or a sulphonylurea) resulted in statistically significant improvements from baseline in HbA1c and FPG at Week 26 when compared to the addition of placebo (Table 2). Clinically meaningful reductions in HbA1c compared to placebo were also observed with NESINA 25 mg regardless of whether patients were receiving concomitant metformin or sulphonylurea therapy. Significantly more patients receiving NESINA 25 mg (49.2%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (34.0%) at Week 26 (p=0.004). Also, fewer patients receiving NESINA 25 mg (9.0%) required hyperglycaemic rescue compared to those receiving placebo (12.4%) during the study.

Improvements in HbA1c were not affected by gender, age, race, baseline BMI, or baseline pioglitazone dose. Patients who entered the study with a higher baseline HbA1c level generally achieved a greater treatment effect. An analysis by baseline HbA1c demonstrated that patients who entered the study with a HbA1c ≥ 8% achieved a significant mean reduction from baseline of -1.1% on NESINA 25 mg versus -0.3% on placebo at Week 26. Compared to placebo, clinically meaningful reductions in HbA1c were also observed with NESINA 25 mg regardless of whether subjects were receiving concomitant metformin or sulfonylurea therapy. There was no significant difference in body weight change between NESINA and placebo when given in combination with pioglitazone. Lipid effects were generally neutral.

NESINA as add-on therapy to a thiazolidinedione with metformin (Study 01-06-TL-322OPI-004)

The addition of NESINA 25 mg once daily to 30 mg pioglitazone and metformin therapy (mean dose = 1867.9 mg) resulted in improvements from baseline in HbA1c at Week 52 that were both non inferior and statistically superior to those produced by 45 mg pioglitazone and metformin therapy (mean dose = 1847.6 mg, Table 3). The significant reductions in HbA1c observed with NESINA 25 mg 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). In addition, mean change from baseline in FPG at Week 52 for NESINA 25 mg plus 30 mg pioglitazone and metformin was significantly greater than that for 45 mg pioglitazone and metformin ($p<0.001$). Significantly more patients receiving NESINA 25 mg plus 30 mg pioglitazone and metformin (33.2%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving 45 mg pioglitazone and metformin (21.3%) at Week 52 ($p<0.001$). Also, fewer patients receiving NESINA 25 mg plus 30 mg pioglitazone and metformin (10.9%) required hyperglycaemic rescue compared to those receiving 45 mg pioglitazone and metformin (21.7%) during the study ($p<0.001$).

Improvements in HbA1c were not affected by gender, age, race or baseline BMI. Patients who entered the study with a higher baseline HbA1c level generally achieved a greater treatment effect. An analysis by baseline HbA1c demonstrated that patients who entered the study with HbA1c ≥ 8% and HbA1c ≥ 9% achieved significant mean reductions from baseline of -1% and -1.3% with NESINA 25 mg in combination with pioglitazone 30 mg and metformin compared to -0.5% in patients receiving a dose titration of pioglitazone from 30 to 45 mg in combination with metformin. A greater increase in body weight was observed in patients receiving a dose titration of pioglitazone from 30 mg to 45 mg in combination with metformin compared to patients receiving NESINA 25 mg in combination with pioglitazone 30 mg and metformin, although there was no significant difference between treatment groups. Lipid effects were generally neutral.

NESINA as add-on therapy to insulin (with or without metformin) (Study SYR-322-INS-011)

The addition of NESINA 25 mg once daily to insulin therapy (mean dose = 56.5 IU, with or without metformin) resulted in statistically significant improvements from baseline in HbA1c and FPG at Week 26 when compared to the addition of placebo (Table 2). Clinically meaningful reductions in HbA1c compared to placebo were also observed with NESINA 25 mg regardless of whether patients were receiving concomitant metformin therapy. More patients receiving NESINA 25 mg (7.8%)

achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (0.8%) at Week 26. Also, significantly fewer patients receiving NESINA 25 mg (19.4%) required hyperglycaemic rescue compared to those receiving placebo (40.0%) during the study (p<0.001).

Improvements in HbA1c were not affected by gender, age, race, baseline BMI, or baseline insulin dose. Patients who entered the study with a higher baseline HbA1c level generally achieved a greater treatment effect. An analysis by baseline HbA1c demonstrated that patients who entered the study with a HbA1c ≥ 9% achieved significant reductions from baseline of -0.8% on NESINA 25 mg versus -0.3% with placebo at Week 26. Compared to placebo, clinically meaningful reductions in HbA1c were also observed with NESINA 25 mg regardless of whether patients were also receiving concomitant metformin therapy. Body weight changes were similar between NESINA 25 mg and placebo when given in combination with insulin. Lipid effects were generally neutral.

Table 2 Change in HbA1c (%) from baseline with NESINA 25 mg at Week 26 by placebo- or active-controlled study (FAS, LOCF)

Study	**FAS patients (n)**	**Mean baseline HbA1c (%) (SD)**	**Least squares mean change from baseline in HbA1c (%) (SE)**	**Treatment-corrected least squares mean change from baseline in HbA1c (%) (2-sided 95% CI)**	**Statistical significance compared to placebo / active-control**
Add-on combination therapy with metformin, or SU, or insulin (with or without metformin) [placebo-controlled]					
NESINA 25 mg once daily with metformin (Study SYR-322-MET-008)	203	7.93 (0.799)	-0.59 (0.054)	-0.48* (-0.67, -0.30)	p<0.001
NESINA 25 mg once daily with a SU (Study SYR-322-SULF-007)	197	8.09 (0.898)	-0.52 (0.058)	-0.53* (-0.73, -0.33)	p<0.001
NESINA 25 mg once daily with insulin (+/-) metformin (Study SYR-322-INS-011)	126	9.27 (1.127)	-0.71 (0.078)	-0.59* (-0.80, -0.37)	p<0.001
Initial combination therapy with TZD factorial study (Study 01-06-TL-322OPI-002)					
NESINA 25 mg once daily					
Overall population	160	8.80 (0.988)	-0.96 (0.081)	-0.75** (-0.98, -0.53)	p<0.001
Baseline HbA1c ≥ 10% stratum	23	10.58 (0.421)	-1.60 (0.326)	-0.56*** (-0.78, -0.33)	p<0.001
NESINA 25 mg & a TZD once daily					
Overall population	158	8.80 (0.962)	-1.71 (0.081)	-1.00** (-1.92, -0.08)	p=0.034
Baseline HbA1c ≥ 10% stratum	24	10.41 (0.246)	-2.60 (0.320)	-0.85*** (-1.76, 0.07)	p=0.070
Add-on combination therapy with TZD (+/-) metformin or a SU (placebo-controlled) (Study SYR-322-TZD-009)					
NESINA 25 mg once daily with a TZD (+/-) metformin or a SU	195	8.01 (0.837)	-0.80 (0.056)	-0.61* (-0.80, -0.41)	p<0.001

FAS = full analysis set
LOCF = last observation carried forward
* = Difference vs placebo
** = Difference vs NESINA 25 mg
*** = Difference vs pioglitazone 30 mg

Table 3 Change in HbA1c (%) from baseline with NESINA 25 mg by active-controlled study (PPS, LOCF)

Study	PPS patients (n)	Mean baseline HbA1c (%) (SD)	Least squares mean change from baseline in HbA1c (%) (SE)	Treatment-corrected least squares mean change from baseline in HbA1c (%) (1-sided CI)
Add-on combination therapy studies				
NESINA 25 mg once daily with metformin vs a SU & metformin (Study SYR-322-305)				
Change at Week 52	537	7.67 (0.527)	-0.61 (0.030)	-0.09[#] (-infinity, 0.004)*
Change at Week 104	382	7.61 (0.526)	-0.72 (0.037)	-0.13[####] (-infinity, -0.006)
NESINA 25 mg once daily with a TZD & metformin vs titrating TZD & metformin (Study 01-06-TL-322OPI-004)				
Change at Week 26	303	8.25 (0.820)	-0.89 (0.042)	-0.47[##] (-infinity, -0.35)**
Change at Week 52	303	8.25 (0.820)	-0.70 (0.048)	-0.42[###] (-infinity, -0.28)**

PPS = per protocol set
[#]Non-inferior to SU + metformin at the 0.0125 1-sided significance level
* = 98.75% 1-sided CI.
[##]Non-inferior to metformin + pioglitazone at the 0.025 1-sided significance level; statistical superiority was not tested
** = 97.5% 1-sided CI.
[###]Non-inferior and statistically superior to metformin + pioglitazone at the 0.025 1-sided significance level
[####]Non inferiority and superiority statistically demonstrated at the 0.025 1-sided significance level

Patients with renal impairment

The efficacy of the recommended doses of NESINA in patients with type 2 diabetes mellitus and renal impairment from the results of Study 402 (n=1880 with mild renal impairment [926 placebo, 954 alogliptin], n=1070 with moderate renal impairment [532 placebo, 538 alogliptin], and n=117 with severe renal impairment or end-stage renal disease [53 placebo, 64 alogliptin]) was reviewed and found to be consistent with the efficacy profile obtained in patients with normal renal function (n=2313 [1168 placebo, 1145 alogliptin]) (see Sections 5.2 Pharmacokinetic Properties, Special Populations, Renal Impairment and 4.2 Dose and Method of Administration).

Elderly patients (≥ 65 years old) (Study SYR-322-303)

Treatment with NESINA 25 mg once daily resulted in improvements from baseline in HbA1c at Week 52 that were non-inferior to those produced by glipizide (mean dose = 5.4 mg). Importantly, despite NESINA and glipizide having similar HbA1c and FPG changes from baseline, episodes of hypoglycaemia were notably less frequent in patients receiving NESINA 25 mg (5.4%) compared to those receiving glipizide (26.0%).

In addition, the efficacy and safety of the recommended doses of NESINA in a subgroup of patients with type 2 diabetes mellitus and ≥ 65 years old were reviewed and found to be consistent with the profile obtained in patients < 65 years old.

Cardiovascular Outcomes (EXAMINE study)

A prospective randomized cardiovascular outcomes safety study was conducted with 5380 type 2 diabetes patients 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 in patients with a recent (15 to 90 days) acute coronary event. In addition to the recent ACS event, the patients in this study were at higher risk for a cardiovascular event with a history of: myocardial infarction (88%), congestive heart failure (27.9%), unstable angina (31.1%), cerebrovascular accident (7.2%), hypertension (83.1%), dyslipidaemias (57.2%) and renal impairment (moderate: 26.2%; severe/end/stage renal disease: 2.9%). At baseline, patients had a mean age of 61 years, mean duration of diabetes of 9.2 years, and mean HbA1c of 8.0%. All subjects received concomitant medications during the study, primarily antidiabetic agents. Nearly half of subjects received triple therapy antidiabetic medications, with approximately one-quarter of subjects having received alogliptin with metformin and a sulphonylurea.

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 **4**).

Table 4 MACE Reported in cardiovascular outcomes study

	Number of Patients (%)	
	Alogliptin 25 mg	**Placebo**
	N=2701	N=2679
Primary Composite Endpoint [First Event of CV Death, Nonfatal MI and Nonfatal Stroke]	**305 (11.3)**	**316 (11.8)**
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].

Overall during the study there were 153 subjects (5.7%) in the alogliptin group and 173 subjects (6.5%) in the placebo group who died. Of those, 112 patients (4.1%) in the alogliptin group had a cardiovascular death (including those that occurred after a first event of myocardial infarction and/or stroke) compared to 130 subjects (4.9%) receiving placebo [Hazard Ratio = 0.851; 2-sided 95% Confidence Interval: 0.662, 1.096].

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of NESINA have been studied in healthy subjects and in patients with type 2 diabetes mellitus, and have been shown to be generally similar.

Absorption

The absolute bioavailability of NESINA 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.

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 Tmax) after dosing.

No clinically relevant accumulation after multiple dosing was observed in either healthy subjects or in patients with type 2 diabetes mellitus.

Total and peak exposure to alogliptin increased proportionally across single doses of up to 100 mg alogliptin. The inter-subject coefficient of variation for alogliptin AUC was small (17%).

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 60-71% of the dose is excreted as unchanged drug in the urine.

Two minor metabolites were detected following administration of an oral dose of [14C] 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 with equal potency 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.

In vitro studies indicate that alogliptin does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP3A4 and does not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at concentrations achieved with the recommended dose of 25 mg 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.

Excretion

The recommended daily dose of NESINA 25 mg was eliminated with a mean terminal half-life ($T_{1/2}$) of approximately 21 hours.

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 faeces.

Linearity

Total exposure (AUC(0-inf)) to alogliptin following administration of a single dose was similar to exposure during one dose interval (AUC(0-24)) after 6 days of once daily dosing. This indicates linear kinetics of alogliptin after multiple dosing.

Special populations

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. Six patients were included in each of the 4 groups.

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 Section 4.2 Dose and Method of Administration).

In patients with moderate or severe renal impairment, or ESRD on haemodialysis, an increase in systemic exposure to alogliptin of approximately 2 and 4-fold was observed, respectively. Patients with ESRD underwent haemodialysis immediately after alogliptin dosing. Based on mean dialysate concentrations, approximately 7% of the drug was removed during a 3-hour haemodialysis session. Therefore, in order to maintain systemic exposures to NESINA that are similar to those observed in patients with normal renal function, lower doses of NESINA should be used in patients with moderate or severe renal impairment, or ESRD requiring dialysis (see Section 4.2 Dose and Method of Administration).

There was no significant difference in exposure to the active metabolite, M-I (< 1% of the parent compound), in patients with mild renal impairment compared to control subjects. Total exposure to M-I was approximately 2- and 3-fold higher in patients with moderate or severe renal impairment, respectively. However, the ratios of AUC for M I/alogliptin in control subjects and patients with severe renal impairment or ESRD were similar.

Hepatic impairment

Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment compared to healthy control subjects. The magnitude of these reductions was not considered to be clinically relevant. Therefore, 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, see Section 4.2 Dose and Method of Administration).

Age, gender, race, body weight

Age (≥ 65 years old), gender, race (white, black and Asian) and body weight did not have any clinically relevant effect on the pharmacokinetics of alogliptin. No dose adjustment is necessary (see Section 4.2 Dose and Method of Administration).

Paediatric population

The pharmacokinetics of alogliptin in patients < 18 years old have not yet been established. No data are available (see Section 4.2 Dose and Method of Administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Alogliptin was not genotoxic in the Ames test, the forward mutation test in mouse lymphoma cells, and the mouse micronucleus test.

Carcinogenicity

In the 2-year study in rats, a dose-related increase in thyroid C-cell adenomas and carcinomas was seen in males only at oral doses greater than or equal to 400 mg/kg/day (at least 240-fold the exposure in humans at the recommended dose of 25 mg). Exposure at the no effect level (75 mg/kg/day) was 27 fold the maximum recommended clinical dose of 25 mg, based on AUC. There was no evidence of a drug-related increase in tumour incidence in female rats or mice of both

sexes treated for 2 years with doses up to 800 mg/kg/day and 300 mg/kg/day, respectively, alogliptin (400-fold and 51-fold, respectively, the exposure in humans at the recommended dose of 25 mg).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet contains the following inactive ingredients: mannitol, microcrystalline cellulose, hyprolose, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide (E171), iron oxide red CI77491 (6.25 mg and 25 mg tablets), iron oxide yellow CI77492 (12.5 mg tablets), macrogol, Edible Ink Gray F1 (PI 108445).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

NESINA is available in blister packs containing 7, 10, 14, 28, 30, 56, 60, 90, 98 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

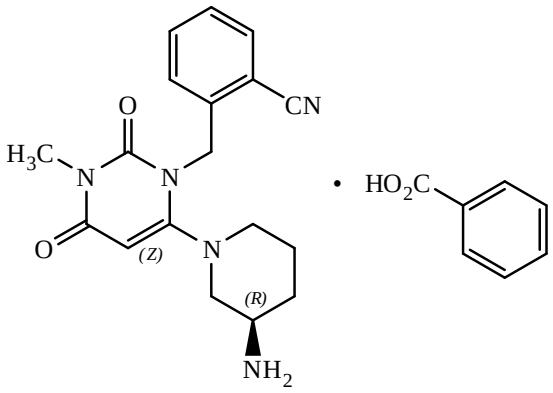
6.7 PHYSICOCHEMICAL PROPERTIES

Alogliptin (MW=339.39, freebase) is an orally bioavailable inhibitor of the enzymatic activity of DPP-4. Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile monobenzoate.

Alogliptin benzoate is a white to off-white, crystalline powder, containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethyl sulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate. The partition coefficient ($C_{1\text{-octanol}}/C_{aqueous}$) of alogliptin benzoate at 25°C and pH 7.4 is -0.5. The pKa is 8.5.

Chemical structure

The structural formula of alogliptin benzoate is:



Molecular formula: $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$

Molecular weight: 461.51

CAS number

850649-62-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

17 September 2013

10 DATE OF REVISION

16 September 2021

Summary table of changes

Section changed	Summary of new information
4.8	Addition of tubulointerstitial nephritis