AUSTRALIAN PRODUCT INFORMATION

NESINA MET® 12.5 mg/500 mg, 12.5 mg/850 mg & 12.5 mg/1000 mg (ALOGLIPTIN / METFORMIN HYDROCHLORIDE)

1 NAME OF THE MEDICINE

NESINA MET tablets contain 2 oral antihyperglycaemic drugs used in the management of type 2 diabetes: alogliptin (as benzoate), a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NESINA MET is available as film-coated tablets for oral administration containing alogliptin benzoate equivalent to 12.5 mg alogliptin free base and:

- 500 mg metformin hydrochloride (12.5 mg/500 mg) or
- 850 mg metformin hydrochloride (12.5 mg/850 mg) or
- 1000 mg metformin hydrochloride (12.5 mg/1000 mg)

Contains benzoates.

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

3 PHARMACEUTICAL FORM

NESINA MET is available in the following presentations:

NESINA MET 12.5/500 film-coated tablets: Pale yellow, oblong, biconvex, film-coated tablet with “12.5/500” debossed on one side and “322M” debossed on the other side

NESINA MET 12.5/850 film-coated tablets: Light yellow, oblong, biconvex, film-coated tablets with “12.5/850” debossed on one side and “322M” debossed on the other side.

NESINA MET 12.5/1000 film-coated tablets: Pale yellow, oblong, biconvex, film-coated tablets with “12.5/1000” debossed on one side and “322M” debossed on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NESINA MET 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 and treatment with both alogliptin and metformin is appropriate,

- when treatment with metformin alone does not provide adequate control; or
- in combination with a thiazolidinedione or with insulin, when dual therapy does not provide adequate control.

NESINA MET can also be used to replace separate tablets of alogliptin and metformin in patients already being treated with this combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and the use of high doses of metformin above 2000 mg per day.

NESINA MET should be taken orally twice daily with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin. 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 at the same time.

To minimise the risk of lactic acidosis and accidental overdosing, patients should be advised to discard their previous metformin and/or alogliptin containing medications.

Adults (≥ 18 years old)

The recommended starting dose of NESINA MET should be individualized based on the patient's current regimen. Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin hydrochloride. NESINA MET is not indicated for initial combination therapy.

Patients inadequately controlled on metformin alone

For patients inadequately controlled on metformin alone, the recommended dose of NESINA MET should provide alogliptin dosed at 12.5 mg twice daily (25 mg total daily dose) and metformin hydrochloride at a similar dose (either 500 mg, 850 mg or 1000 mg twice daily) to that already being taken.

Patients inadequately controlled on dual therapy with metformin and a thiazolidinedione

For patients inadequately controlled on dual therapy with metformin and a thiazolidinedione, the dose of the thiazolidinedione should be maintained, and NESINA MET administered concomitantly; alogliptin should be dosed at 12.5 mg twice daily (25 mg total daily dose) and metformin hydrochloride at a similar dose (either 500 mg, 850 mg or 1000 mg twice daily) to that already being taken.

Patients inadequately controlled on dual combination therapy with insulin and metformin

For patients inadequately controlled on dual combination therapy with insulin and metformin, the dose of NESINA MET should provide alogliptin dosed at 12.5 mg twice daily (25 mg total daily dose) and a dose of metformin similar to the dose already being taken. A lower dose of insulin may be considered to reduce the risk of hypoglycaemia.

Patients switching from separate tablets of alogliptin and metformin

For patients switching from separate tablets of alogliptin and metformin, both alogliptin and metformin should be dosed at the total daily dose already being taken; the individual dose of alogliptin should be halved as it will be taken twice daily whilst the dosing of metformin (either 500 mg, 850 mg or 1000 mg twice daily) should remain unchanged.

Special populations

Hepatic impairment

Due to its metformin component, NESINA MET should not be used in patients with hepatic impairment (see Section 4.4 Special Warnings and Precautions for Use).

Renal impairment

For patients with mild renal impairment, no dose adjustment of NESINA MET is necessary (see Section 5.2 Pharmacokinetic Properties, Special Populations).

Due to its metformin component, NESINA MET should not be used in patients with moderate or severe renal impairment (see Section 4.3 Contraindications).

Appropriate assessment of renal function is recommended prior to initiation of NESINA MET and at regular intervals thereafter (see Section 4.4 Special Warnings and Precautions for Use).

Elderly (≥ 65 years old)

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

Paediatric population

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

4.3 CONTRAINDICATIONS

NESINA MET is contraindicated in patients with:

- Renal disease or dysfunction (e.g. as suggested by serum creatinine levels ≥ 135 µmol/L for men, ≥ 110 µmol/L for women or creatinine clearance < 60 mL/min) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia (see Section 4.4 Special Warnings and Precautions for Use).
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, diabetic coma or pre-coma. Diabetic ketoacidosis should be treated with insulin.
- Known hypersensitivity to alogliptin benzoate, metformin hydrochloride or any of the excipients.

NESINA MET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see Section 4.4 Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

NESINA MET should not be used in patients with type 1 diabetes mellitus.

Lactic acidosis

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic impairment and any conditions associated with hypoxia.

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with NESINA MET should be discontinued and the patient hospitalised immediately.

Patients with known or suspected mitochondrial diseases

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Monitoring of renal function

Renal function should be confirmed before initiation of NESINA MET therapy, and then at least once a year in patients with normal renal function and at least two to four times a year in patients with serum creatinine levels at or above the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Use of concomitant medications that may affect renal function or metformin disposition

Concomitant medication(s) that may affect renal function, result in significant haemodynamic change or interfere with the disposition of metformin hydrochloride, such as cationic drugs that are eliminated by renal tubular secretion should be used with caution (see Section 4.5 Interactions With Other Medicines and Other Forms of Interaction).

Intravascular administration of iodinated contrast agents

The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving metformin. Therefore, NESINA MET should be discontinued prior to, or at the time of, the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see Sections 4.3 Contraindications and 4.5 Interaction With Other Medicines and Other Forms of Interactions).

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur in patients on NESINA MET therapy, the drug should be promptly discontinued.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving NESINA MET.

Surgery

As NESINA MET contains metformin, treatment should be discontinued 48 hours before elective surgery with general, spinal or epidural anaesthesia. Treatment should not usually be resumed earlier than 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Vitamin B12 Levels

In controlled, 29-week clinical trials of immediate release metformin, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in

approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on NESINA MET and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

Use with other antihyperglycaemic medications and hypoglycaemia

A clinical trial of alogliptin as add-on therapy to metformin demonstrated that there was no clinically relevant increase in hypoglycaemia rate compared to placebo. The incidence of hypoglycaemia was greater in studies of alogliptin as add-on therapy to metformin with a thiazolidinedione and as add-on therapy to metformin with insulin 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 NESINA MET (see Section 4.2 Dose and Method of Administration).

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

Change in clinical status of patients with previously controlled type 2 diabetes mellitus

As NESINA MET contains metformin, any patient with type 2 diabetes mellitus previously well controlled on NESINA MET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis.

Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, NESINA MET must be stopped immediately and other appropriate corrective measures initiated.

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, NESINA MET 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, NESINA MET 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 treatment with NESINA MET.

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 MET. If bullous pemphigoid is suspected, NESINA MET should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Use in hepatic impairment

Because impaired hepatic function has been associated with some cases of lactic acidosis, NESINA MET should not be used in patients with clinical or laboratory evidence of hepatic disease.

Use in renal impairment

Alogliptin and metformin are substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Thus, patients with raised serum creatinine levels (e.g. serum creatinine levels ≥ 135 µmol/L for men, ≥ 110 µmol/L for women or creatinine clearance < 60 mL/min) should not receive alogliptin and metformin (see Section 4.3 Contraindications).

Use in the elderly

As metformin is excreted via the kidney, and elderly patients have a tendency to have decreased renal function, elderly patients taking NESINA MET should have their renal function monitored regularly. NESINA MET should only be used in elderly patients with normal renal function (see Section 4.3 Contraindications).

Paediatric use

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

Effects on laboratory tests

<u>Alogliptin and Metformin</u>

No clinically meaningful differences were observed among treatment groups regarding haematology, serum chemistry, or urinalysis results.

<u>Alogliptin</u>

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

<u>Metformin</u>

Metformin may lower serum Vitamin B12 concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on NESINA MET and any apparent abnormalities should be appropriately investigated and managed (see Section 4.4 Special Warnings and Precautions for Use).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Alogliptin and Metformin

Coadministration of 100 mg alogliptin once daily and 1000 mg metformin hydrochloride twice daily for 6 days in healthy subjects had no clinically relevant effects on the pharmacokinetics of alogliptin or metformin.

Specific pharmacokinetic drug interaction studies have not been performed with NESINA MET. The following section outlines the interactions observed with the individual components of NESINA MET (alogliptin/metformin).

Interactions with alogliptin

Alogliptin 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 alogliptin is recommended based on results of the described pharmacokinetic studies.

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

Pioglitazone: Administration of 25 mg of alogliptin 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 25 mg of alogliptin 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 25 mg of alogliptin 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 25 mg of alogliptin 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.

Interactions with metformin

Frusemide

Frusemide increased C_{max} and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased C_{max}, blood AUC of frusemide, with no change in renal clearance of frusemide.

Nifedipine

Nifedipine increased absorption, C_{max} and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.

Glimepiride

Glimepiride produced no changes in metformin PK/PD parameters. Decreases in C_{max}, blood AUC of glimepiride were observed, but were highly variable. Therefore the clinical significance of this finding was unclear.

Cationic drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically

have the potential for interaction with metformin by competing for common renal tubular transport systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60% and 40% respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin and such medications are recommended.

Other

Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Close monitoring of glycaemic control and metformin dose adjustments are recommended when such drugs are administered or withdrawn for these patients.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of NESINA MET. Consumption of alcohol and medicinal products containing alcohol should be avoided (see Section 4.4 Special Warnings and Precautions for Use).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of NESINA MET on fertility in humans has not been studied. No adverse effects on fertility were observed in animal studies conducted with alogliptin or with metformin.

Alogliptin

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.

Metformin

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Use in pregnancy (Category C)

There are no adequate and well-controlled studies in pregnant women with NESINA MET or its individual components. Because animal reproduction studies are not always predictive of a human response, NESINA MET should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

No treatment-related fetal abnormalities occurred following concomitant administration of 100 mg/kg/day alogliptin with 150 mg/kg/day metformin to pregnant rats. These doses produced estimated exposure margins of 29-fold for alogliptin and 3 fold for metformin at the maximum recommended human dose (MRHD) of 25 mg/day and 2000 mg/day, respectively. At notably higher doses of metformin (500 mg/kg/day) administered concomitantly with the same 100 mg/kg/day alogliptin dose, 5 abnormal fetuses were noted in 2 litters (4 fetuses from the same litter). This dose combination produced estimated exposure margins of 20 fold and 8-fold the exposure seen at the MRHD for alogliptin and metformin, respectively.

Use in lactation

No studies have been conducted with the combined components of NESINA MET. In studies performed with the individual components, both alogliptin and metformin are secreted in the milk of

lactating rats. It is not known whether alogliptin is secreted in human milk; some excretion of metformin in human milk has been observed. Therefore, NESINA MET should not be used by nursing women.

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 studies conducted to support the efficacy and safety of NESINA MET involved the coadministration of alogliptin and metformin as separate tablets. However, the results of bioequivalence studies have demonstrated that NESINA MET film-coated tablets are bioequivalent to the corresponding doses of alogliptin and metformin co-administered as separate tablets.

A total of 7150 patients with type 2 diabetes mellitus, including 4201 patients treated with alogliptin and metformin, participated in 7 phase 3 double-blind, placebo- or active-controlled clinical studies. These studies evaluated the effects of coadministered alogliptin and metformin on glycaemic control and their safety in a number of settings, including dual therapy in patients initially treated with metformin alone and as add-on therapy to a thiazolidinedione or insulin.

The safety profile of coadministered alogliptin and metformin was consistent with that of the individual components as demonstrated in clinical trials for alogliptin and from the comprehensive data available for metformin. The following section outlines the undesirable effects of the individual components of NESINA MET (alogliptin/metformin).

Clinical Trials Experience

Alogliptin

The information provided is based on a total of 9405 patients with type 2 diabetes mellitus, including 3750 patients treated with 25 mg alogliptin and 2476 patients treated with 12.5 mg alogliptin, 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 alogliptin on glycaemic control and its safety as monotherapy, in 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 25 mg alogliptin, 12.5 mg alogliptin, active-control or placebo. The most common adverse reaction in patients treated with alogliptin 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 25 mg alogliptin than in patients treated with 12.5 mg alogliptin, 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 25 mg alogliptin or 12.5 mg alogliptin, 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, alogliptin 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 25 mg alogliptin (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 25 mg alogliptin, 12.5 mg alogliptin, 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).

Metformin

Clinical trial data and post-marketing experience

Table 2 Frequency of metformin adverse reactions identified from clinical trial data and post-marketing experience

System organ class Adverse reaction	Metformin monotherapy
Metabolism and nutrition disorders	
Lactic acidosis[1]	Very rare
Vitamin B12 deficiency[2]	Very rare
Nervous system disorders	
Metallic taste	Common
Gastrointestinal disorders[3]	
Abdominal pain	Very common
Diarrhoea	Very common
Loss of appetite	Very common
Nausea	Very common
Vomiting	Very common
Hepatobiliary disorders[4]	
Hepatitis	Very rare
Liver function test abnormalities	Very rare
Skin and subcutaneous tissue disorders	
Erythema	Very rare
Pruritus	Very rare
Urticaria	Very rare
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)

[1] 0.03 cases/1000 patient-years.

[2] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption and appears generally to be without clinical significance. However, it may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

[3] Gastrointestinal symptoms occur most frequently during initiation of therapy and resolve spontaneously in most cases. These may be prevented by taking metformin in 2 daily doses during or after meals.

[4] Isolated cases of hepatitis or liver function test abnormalities resolving on discontinuation of metformin have been reported.

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 data are available with regard to overdose of NESINA MET.

Alogliptin

No adverse events associated with overdose of alogliptin 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 total daily dose of 25 mg alogliptin, respectively). No serious adverse events were observed at these dose levels.

In the event of an alogliptin 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.

Metformin

Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

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

NESINA MET combines two antihyperglycaemic medications with complementary and distinct mechanisms of action to improve glycaemic control in patients with type 2 diabetes mellitus: alogliptin, a dipeptidyl-peptidase-4 (DPP-4) inhibitor, and metformin, a member of the biguanide class.

Alogliptin

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 total daily dose of 25 mg alogliptin. 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 25 mg of 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, 14 days of treatment with 25 mg of alogliptin resulted in a mean placebo-corrected reduction from baseline of -1.95 mmol/L.

Both 25 mg alogliptin 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, 25 mg alogliptin 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.

Cardiac Electrophysiology

In a randomized, placebo-controlled, 4-arm, parallel-group study, 257 subjects were administered either alogliptin 50 mg, alogliptin 400 mg, moxifloxacin 400 mg, or placebo once-daily for a total of 7 days. No increase in QTc was observed with either dose of alogliptin (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.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- by reducing hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical trials

The clinical studies conducted to support the efficacy of NESINA MET involved the coadministration of alogliptin and metformin as separate tablets. There have been no clinical efficacy studies conducted with NESINA MET tablets; however, the results of bioequivalence studies have demonstrated that NESINA MET film-coated tablets are bioequivalent to the corresponding doses of alogliptin and metformin coadministered as separate tablets.

The coadministration of alogliptin and metformin has been studied in a number of settings, including dual therapy in patients initially treated with metformin alone and as add-on therapy to a thiazolidinedione or insulin.

A total of 7150 patients with type 2 diabetes mellitus, including 4201 patients treated with alogliptin and metformin, participated in 7 phase 3 double-blind, placebo- or active-controlled clinical studies

conducted to evaluate the effects of coadministered alogliptin and metformin on glycaemic control and their safety. In these studies, 696 alogliptin/metformin-treated patients were ≥ 65 years old.

Overall, treatment with the recommended total daily dose of 25 mg alogliptin in combination with metformin improved glycaemic control. 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 age, gender, race and body mass index (BMI). Clinically meaningful reductions in HbA1c compared to control were also observed regardless of baseline background medication dose. 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 add-on therapy to metformin

The addition of 25 mg alogliptin once daily to metformin hydrochloride 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 3) (Study SYR-322-MET-008). Significantly more patients receiving 25 mg alogliptin (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 25 mg alogliptin (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 25 mg alogliptin versus -0.3% and 0.5% on placebo at Week 26, respectively. A similar decrease in body weight was observed for both alogliptin 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 alogliptin 25 mg versus glipizide to metformin therapy, the addition of 25 mg alogliptin once daily to metformin hydrochloride 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 4) 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 4) 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 alogliptin 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 alogliptin 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 + 25 mg alogliptin treatment group compared with the metformin + glipizide treatment group ($p\leq0.05$).

Alogliptin as add-on therapy to metformin with a thiazolidinedione (TZD)

The addition of 25 mg alogliptin 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 3) (Study SYR-322-TZD-009). Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin or sulphonylurea therapy. Significantly more patients receiving 25 mg alogliptin (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 25 mg alogliptin (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 25 mg alogliptin versus -0.3% on placebo at Week 26. Compared to placebo, clinically meaningful reductions in HbA1c were also observed with 25 mg alogliptin regardless of whether subjects were receiving concomitant metformin or sulfonylurea therapy. There was no significant difference in body weight change between alogliptin and placebo when given in combination with pioglitazone. Lipid effects were generally neutral.

In another study, the addition of 25 mg alogliptin once daily to 30 mg pioglitazone in combination with metformin hydrochloride 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 in combination with metformin hydrochloride therapy (mean dose = 1847.6 mg, (Table 4) (Study 01-06-TL-322OPI-004). 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). In addition, mean change from baseline in FPG at Week 52 for 25 mg alogliptin plus 30 mg pioglitazone and metformin was significantly greater than that for 45 mg pioglitazone and metformin ($p<0.001$). Significantly more patients receiving 25 mg alogliptin 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 25 mg alogliptin 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 25 mg alogliptin 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 25 mg alogliptin in combination with pioglitazone 30 mg and metformin, although there was no significant difference between treatment groups. Lipid effects were generally neutral.

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

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 and FPG at Week 26 when compared to the addition of placebo (Table 3). Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin therapy. More patients receiving 25 mg alogliptin (7.8%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (0.8%) at Week 26.

Also, significantly fewer patients receiving 25 mg alogliptin (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 25 mg alogliptin versus -0.3% with placebo at Week 26. Compared to placebo, clinically meaningful reductions in HbA1c were also observed with 25 mg alogliptin regardless of whether patients were also receiving concomitant metformin therapy. Body weight changes were similar between 25 mg alogliptin and placebo when given in combination with insulin. Lipid effects were generally neutral.

Table 3 Change in HbA1c (%) from baseline with alogliptin 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 placebo-controlled studies					
alogliptin 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
alogliptin 25 mg once daily with a TZD (+/-) metformin or a SU *(Study SYR-322-TZD-009)*	195	8.01 (0.837)	-0.80 (0.056)	-0.61* (-0.80, -0.41)	p<0.001
alogliptin 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
FAS = full analysis set LOCF = last observation carried forward			* = difference vs placebo		

Table 4 Change in HbA1c (%) from baseline with alogliptin 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				
alogliptin 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)
alogliptin 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.				

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)
##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				

Cardiovascular Outcomes (EXAMINE study)

A prospective randomized cardiovascular outcomes safety study was conducted with 5380 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 type 2 diabetes and 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 **5**).

Table 5 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].

Therapeutic Equivalence of Alogliptin Divided Dosing (Study SYR322MET_302)

In a 26-week, double-blind, placebo-controlled study, a total of 784 patients inadequately controlled on diet and exercise alone (mean baseline A1C=8.4%) were randomized to 1 of 7 treatment groups: placebo; metformin 500 mg or metformin 1000 mg twice daily (BID), alogliptin 12.5 mg twice daily (BID), or alogliptin 25 mg daily (QD); alogliptin 12.5 mg in combination with metformin 500 mg or metformin 1000 mg twice daily (BID). Results demonstrated therapeutic equivalence between alogliptin 12.5 mg BID vs. 25 mg QD dosing with respect to reduction in HbA1c% (-0.04; 95%CI -0.30, +0.22). Additionally, statistically significant and clinical meaningful reduction in HbA1c% was achieved with alogliptin 12.5 mg add-on to metformin 500 mg or 1000 mg BID (-0.57; 95%CI -0.87, -0.27 and -0.44; 95%CI 0.73, -0.16 respectively). The estimate of placebo-corrected treatment effect of alogliptin/metformin 12.5/500 or 12.5/1000 BID treatment on HbA1C% reduction was -1.37 (95%CI -1.63, -1.11) and -1.70 (95%CI -1.96, -1.45), respectively.

5.2 PHARMACOKINETIC PROPERTIES

In bioequivalence studies of NESINA MET, the area under the curve (AUC) and maximum concentration (C_{max}) of both the alogliptin and the metformin component following a single dose of the combination tablet were bioequivalent to the alogliptin 12.5 mg concomitantly administered with metformin hydrochloride 500 or 1000 mg tablets under fasted conditions in healthy subjects.

Coadministration of 100 mg alogliptin once daily and 1000 mg metformin hydrochloride twice daily for 6 days in healthy subjects had no clinically relevant effects on the pharmacokinetics of alogliptin or metformin.

Administration of NESINA MET with food resulted in no change in total exposure (AUC) to alogliptin or metformin. However, mean peak plasma concentrations of alogliptin and metformin were decreased by 13% and 28% when NESINA MET was administered with food, respectively. There was no change in the time to peak plasma concentration (T_{max}) for alogliptin, but there was a delayed T_{max} for metformin of 1.5 hours. These changes are not likely to be clinically significant.

NESINA MET should be taken twice daily because of the pharmacokinetics of its metformin component. It should also be taken with meals to reduce the gastrointestinal undesirable effects associated with metformin (see Section 4.2 Dose and Method of Administration).

The pharmacokinetics of NESINA MET in patients < 18 years old have not been established. No data are available.

The following section outlines the pharmacokinetic properties of the individual components of NESINA MET (alogliptin/metformin):

Absorption

Alogliptin

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. Alogliptin 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 T_{max}) 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%).

Metformin

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximate 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve, and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Alogliptin

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.

Metformin

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 L. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally < 1 microgram/mL. During controlled clinical trials of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 microgram/mL, even at maximum doses.

Metabolism

Alogliptin

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 [^{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 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.

Metformin

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion

Alogliptin

The recommended total daily dose of 25 mg alogliptin 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.

Metformin

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Linearity

Alogliptin

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 days of once daily dosing. This indicates linear kinetics of alogliptin after multiple dosing.

Metformin

Studies using single oral doses of metformin tablets indicate a lack of dose proportionality, due to increased absorption of metformin with increasing doses.

Alogliptin QD vs BID dosing

The multiple-dose pharmacokinetics and pharmacodynamics of alogliptin 12.5 mg twice daily (BID) and alogliptin 25 mg once daily (QD) were compared in a randomized, open-label, crossover study in healthy subjects. Subjects were randomized to 1 of 2 treatment sequences and received alogliptin 25 mg once daily or alogliptin 12.5 mg BID for 7 days. The 90% CI for the ratio of the LS means of AUC(0-24) for the 12.5 mg BID dose to the 25 mg once daily dose was within the 80% to 125% range (97.57, 108.60). Therefore, total exposure from time 0 to 24 hours was similar between the QD and BID dosing regimens. The T_{max} values were also identical for the two regimens (C_{min} and C_{max} differ due to different design and dosing, as expected for a drug with linear pharmacokinetics). Additionally, the pharmacodynamic results showed that the extent of DPP-4 inhibition was similar with BID or QD dosing.

Special populations

Type 2 diabetes

Alogliptin

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

Metformin

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal impairment

Use of NESINA MET in patients with renal impairment increases the risk for lactic acidosis. Because NESINA MET contains metformin, NESINA MET is contraindicated in patients with moderate or severe renal impairment (see Section 4.3 Contraindications).

Alogliptin

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.

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 alogliptin that are similar to those observed in patients with normal renal function, lower doses of alogliptin should be used in patients with moderate or severe renal impairment, or ESRD requiring dialysis.

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.

Metformin

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic impairment

NESINA MET is not recommended in patients with hepatic impairment (see Section 4.4 Special Warnings and Precautions for Use).

Alogliptin

Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment compared to control subjects. The magnitude of these reductions was not considered to be clinically relevant. Therefore, no dose adjustment of alogliptin 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).

Metformin

No pharmacokinetic studies of metformin have been conducted in subjects with hepatic impairment. Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis.

Gender

Alogliptin

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

Metformin

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin hydrochloride tablets was comparable in males and females.

Elderly

Alogliptin

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

Metformin

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

NESINA MET treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see Sections 4.4 Special Warnings and Precautions for Use and 4.2 Dose and Method of Administration).

Paediatric

No studies with NESINA MET have been performed in paediatric patients.

Race

Alogliptin

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

Metformin

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycaemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Body Weight

Body weight did not have any clinically relevant effect on the pharmacokinetics of alogliptin. No dose adjustment of alogliptin and NESINA MET is necessary.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Alogliptin

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

Metformin

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Carcinogenicity

Alogliptin

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).

Metformin

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet contains the following inactive ingredients: mannitol, microcrystalline cellulose, povidone, crospovidone, magnesium stearate, hypromellose, purified talc, titanium dioxide, and iron oxide yellow (CI77492).

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 MET is available in blister packs containing 10, 14, 20, 28, 56, 60, 98, 112, 120, 180, 196 or 200 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

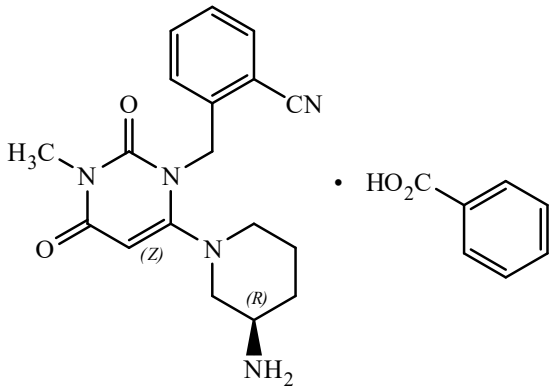
Alogliptin benzoate is a white to off-white, crystalline powder, containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate. The partition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

Metformin hydrochloride is a white, crystalline powder which is odourless or almost odourless and hygroscopic. It is freely soluble in water, slightly soluble in ethanol (96%), and practically insoluble in chloroform and in ether.

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.

Chemical structure



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

Molecular weight: 461.51 (freebase MW=339.39)

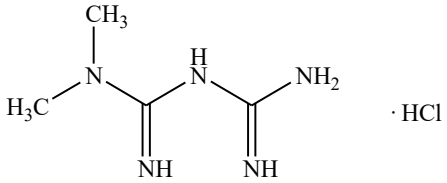
CAS number

850649-62-6

Metformin Hydrochloride

Chemical name: *N,N* -dimethylimidodicarbonimidic diamide hydrochloride

Chemical structure



Molecular formula: $C_4H_{11}N_5$•HCl

Molecular weight: 165.63

CAS number

1115-70-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

22 October 2013

10 DATE OF REVISION

11 February 2026

Summary table of changes

Section changed	Summary of new information
4.4	Addition of warning related to aggravation of MELAS (Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes) syndrome and MIDD (Maternal inherited diabetes and deafness) in patients taking metformin with known mitochondrial diseases as per PRAC recommendation.