AUSTRALIAN PRODUCT INFORMATION

ONGLYZA ®
(saxagliptin) Tablets

1 NAME OF THE MEDICINE

Saxagliptin (as hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of ONGLYZA contains either 2.5 mg or 5 mg of saxagliptin free base (as saxagliptin hydrochloride).

Excipients with known effect: lactose monohydrate

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

3 PHARMACEUTICAL FORM

Film-coated tablets.

ONGLYZA (saxagliptin) 2.5 mg tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with "2.5" printed on one side and "4214" printed on the other side, in blue ink.

ONGLYZA (saxagliptin) 5 mg tablets are pink, biconvex, round, film-coated tablets with "5" printed on one side and "4215" printed on the other side, in blue ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Add-on combination

ONGLYZA is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicines, when these together with diet and exercise, do not provide adequate glycaemic control (*see Sections 5.1 Pharmacodynamic properties- Clinical Trials* and *4.4 Special warnings and precautions for use* for available data on different add-on combination therapies).

Initial combination

ONGLYZA is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate. (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).

4.2 Dose and method of administration

ONGLYZA tablets must not be split or cut.

ONGLYZA can be taken with or without food.

Add-On Combination Therapy

The recommended dose of ONGLYZA is 5 mg once daily as add-on dual combination therapy with metformin, a thiazolidinedione or a sulfonylurea or as a component of triple oral therapy with metformin and a sulfonylurea or a sodium-glucose co-transporter 2 inhibitor.

In patients with inadequate glycaemic control with premixed or basal insulin (with or without metformin), the recommended dose of ONGLYZA is 5 mg once daily. Patients should be made aware of the potential risk of hypoglycaemia with a change in diabetes regime. ONGLYZA has not been studied in a regimen combining intermediate or long-acting insulin with mealtime bolus doses of short acting insulin (basal:bolus regimens) and its efficacy in this context has not been established. Evaluated experience with insulin is so far limited to 24 weeks of treatment (*see Section 5.1 Pharmacodynamic properties- Clinical Trials*).

Initial Combination Therapy

The recommended starting doses of ONGLYZA and metformin when used as initial combination therapy is 5 mg ONGLYZA plus 500 mg metformin once daily. Patients with inadequate glycaemic control on this starting dose should further have their metformin dose increased according to approved metformin Product Information.

Special patient populations

Renal impairment

Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter *(see Sections 4.4 Special Warnings and Precautions for Use – Use in Renal impairment and 5.2 Pharmacokinetic properties- Special Populations (Renal impairment)).*

Mild renal impairment (eGFR 60-89 mL/min/1.73 m^2)

No dosage adjustment is required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2 (by MDRD eGFR equation))

Moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2)

No dosage adjustment is required for patients with eGFR $\geq$ 45 mL/min/1.73 m^2.

For patients with moderate renal impairment with eGFR < 45 mL/min/1.73 m^2, the dose is 2.5 mg once daily in combination with a sulfonylurea, a thiazolidinedione, or premixed or basal insulin.

Severe renal impairment (eGFR 15-<30 mL/min/1.73 m^2)

For patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), the dose is 2.5 mg once daily. Saxagliptin should be used with caution in patients with severe renal impairment.

ONGLYZA is not recommended for patients with end-stage renal disease (ESRD), an eGFR <15mL/min/1.73 m^2or requiring either hemodialysis or peritoneal dialysis.

Hepatic impairment

No dosage adjustment for ONGLYZA is necessary for patients with mild, moderate, or severe hepatic impairment.

Use in paediatric and adolescent

Safety and effectiveness of ONGLYZA in paediatric and adolescent patients have not been established.

Use in the elderly

No dosage adjustment for ONGLYZA is required based solely on age. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. (*See Section 4.4 Special warnings and precautions for use – Use in the elderly*)

4.3 Contraindications

ONGLYZA is contraindicated in patients with a history of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to any component of ONGLYZA or to any DPP-4 inhibitor.

4.4 Special warnings and precautions for use

General

ONGLYZA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. ONGLYZA has not been studied in combination with GLP-1 agonists (e.g. exenatide, liraglutide).

Hypersensitivity Reactions

During postmarketing experience the following adverse reactions have been reported with use of saxagliptin: serious hypersensitivity reactions, including anaphylaxis and angioedema. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency. If a serious hypersensitivity reaction to saxagliptin is suspected, discontinue ONGLYZA, assess for other potential causes for the event, and institute alternative treatment for diabetes. (*See sections 4.3 Contraindications* and *4.8 Adverse effects (undesirable effects) – Postmarketing experience*.)

Pancreatitis

During postmarketing experience, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, ONGLYZA should be discontinued. (*See section 4.8 Adverse effects (undesirable effects) – Postmarketing experience*.)

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the incidence of adjudicated pancreatitis events was 0.3% in both ONGLYZA treated patients and placebo-treated patients in the intent-to-treat population. (*See Section 4.8 Adverse effects (undesirable effects) – Adverse Reactions Associated with ONGLYZA in the SAVOR trial*.)

Use in renal impairment

Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. No dosage adjustment is required in patients with eGFR $\geq$ 45 mL/min/1.73 m^2. In patients with eGFR < 45 ml/min/1.73m^2, the dose is 2.5 mg once daily. The experience in patients with severe renal impairment is very limited. Saxagliptin should be used with caution in patients with severe renal impairment (eGFR 15–<30 mL/min/1.73 m^2) and is not recommended for use in patients with ESRD. There is insufficient data to recommend use in patients with eGFR< 15 mL/min/1.73m^2 or requiring either hemodialysis or peritoneal dialysis. (*See section 4.2 Dose and method of administration – Special Patient Populations (Use in Renal Impairment)*).

Skin disorders

Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies. Although skin lesions were not observed at an increased incidence in clinical

trials, there is limited experience in patients with diabetic skin complications. Postmarketing reports of rash have been described in the DPP4 inhibitor class. Rash is also noted as an adverse event for saxagliptin (*see section 4.8 Adverse effects (undesirable effects) – Postmarketing experience*). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.

Bullous pemphigoid

Post-marketing 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 ONGLYZA. If bullous pemphigoid is suspected, ONGLYZA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (*see Section 4.8 Adverse effects (undesirable effects) – Postmarketing experience*).

Cardiac failure

Experience in NYHA class III-IV is still limited. In the SAVOR trial a small increase in the rate for hospitalisation for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established (*See Section 5.1 Pharmacodynamic properties – Clinical Trials (Cardiovascular Safety)*). Additional analysis did not indicate a differential effect among NYHA classes. (*See Section 4.8 Adverse effects (undesirable effects) - Adverse Reactions Associated with ONGLYZA in the SAVOR trial*). Caution is warranted if ONGLYZA is used in patients who have known risk factors for hospitalization for heart failure, such as a history of heart failure or moderate to severe renal impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms.

Arthralgia

Joint pain, which may be severe, has been reported in postmarketing reports for DPP4 inhibitors. Patients experienced relief of symptoms after discontinuation of the medication and some experienced recurrence of symptoms with reintroduction of the same or another DPP4 inhibitor. Onset of symptoms following initiation of drug therapy may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of drug therapy should be individually assessed. (*See Section 4.8 Adverse effects (undesirable effects) – Postmarketing experience*).

Immunocompromised patients

Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome, have not been studied in the saxagliptin clinical program. Therefore, the efficacy and safety profile of saxagliptin in these patients has not been established.

Use with Medications Known to Cause Hypoglycaemia

The sulfonylurea class of antihyperglycaemic agents and insulin are known to cause hypoglycaemia. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycaemia when used in combination with ONGLYZA. (*See Section 4.8 Adverse effects (undesirable effects)*.)

Use in the elderly

Saxagliptin and its major metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. (*See Sections 4.2 Dose and method of administration – Special*

Populations (Use in the elderly) and 5.1 Pharmacodynamic properties – Clinical Trials (Elderly patients))

Paediatric use

Safety and effectiveness of ONGLYZA in paediatric patients have not been established.

Effects on Laboratory tests

No data available

4.5 Interactions with other medicines and other forms of interactions

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5) which converts it to an active metabolite. Therefore, drugs which inhibit the activity of this enzyme system may increase plasma concentrations of saxagliptin but reduce those of its metabolite, whereas CYP3A inducers will tend to do the opposite. However, the overall biological effect of saxagliptin is unaffected by coadministration with inhibitors or inducers of CYP3A4/5.

In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4, nor inhibited UGT1A9. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolised by these enzymes. Saxagliptin is neither a significant inhibitor of P-glycoprotein (P-gp) nor an inducer of P-gp.

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is below measurable levels. Thus, protein binding would not have a meaningful influence on the pharmacokinetics of saxagliptin or other drugs.

In studies conducted in healthy subjects, the pharmacokinetics of saxagliptin, and its major metabolite, were altered by some drugs which affect the CYP3A4/5 system. However, total exposure of the total active components of saxagliptin (parent + metabolite), was not meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole, rifampicin, omeprazole, aluminium hydroxide + magnesium hydroxide + simethicone combination, or famotidine. Saxagliptin also did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole or an estrogen/progestin contraceptive.

Other interactions

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of saxagliptin have not been specifically studied.

The safety and efficacy of saxagliptin in combination with alpha-glucosidase inhibitors or orlistat has not been established.

4.6 Fertility, pregnancy and lactation

Effects on fertility

In a rat fertility study, males were treated with oral gavage doses of 100, 200, and 400 mg/kg/day for two weeks prior to mating, during mating, and up to scheduled termination (approximately four weeks total) and females were treated with oral gavage doses of 125, 300, and 750 mg/kg/day for two weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at 200 mg/kg/day (males) or 125 mg/kg/day (females) resulting in respective exposures (AUC) of approximately 670 (males) and 865 (females) times human exposure at the recommended clinical dose. At higher, maternally toxic doses (300 and 750 mg/kg/day), increased fetal resorptions were

observed (approximately 2300 and 6810 times the recommended clinical dose). Additional effects on oestrous cycling, fertility, ovulation, and implantation were observed at 750 mg/kg/day (approximately 6810 times the recommended clinical dose).

Use in pregnancy – Category B3

Saxagliptin was not teratogenic at any dose evaluated in rats or rabbits. At high doses in rats, saxagliptin caused a minor developmental delay in ossification of the foetal pelvis at ≥240 mg/kg/day (≥1670 times the human exposure [AUC] at the recommended clinical dose). Maternal toxicity and reduced foetal body weights were observed at 900 mg/kg/day (>8860 times the recommended clinical dose). In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (200 mg/kg/day, exposures 1520 times the recommended clinical dose).

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (≥250 mg/kg/day, exposures ≥1810 times the recommended clinical dose). No functional or behavioural toxicity was observed in the offspring of rats administered saxagliptin at any dose.

Saxagliptin and/or its metabolites cross the placenta into the fetus following dosing in pregnant rats.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA should be used during pregnancy only if clearly needed.

Use in lactation

Saxagliptin and/or its metabolites are secreted in the milk of lactating rats. It is not known whether saxagliptin is secreted in human milk. Caution should be exercised when ONGLYZA is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that dizziness has been reported with saxagliptin.

4.8 Adverse effects (Undesirable effects)

Significant adverse events are also included in the Precautions sections.

In randomised, controlled, double-blind clinical trials, over 17,000 patients with type 2 diabetes have been treated with ONGLYZA.

Adverse Reactions Associated with ONGLYZA in the SAVOR trial.

The SAVOR trial included 8240 patients treated with ONGLYZA 5 mg or 2.5 mg once daily and 8173 patients on placebo.

The overall incidence of adverse events in patients treated with ONGLYZA in this trial was similar to placebo (72.5% versus 72.2%, respectively).

Hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance favouring placebo [HR = 1.27; 95% CI 1.07, 1.51); p=0.007]. (*See Section 5.1 Pharmacodynamic properties - Clinical Trials (Cardiovascular Safety)*).

In the SAVOR trial, the incidence of adjudicated pancreatitis events was 0.3% in both ONGLYZA-treated patients and placebo-treated patients in the intent-to-treat population.

The incidence of hypersensitivity reactions was 1.1% in both ONGLYZA-treated patients and placebo-treated patients.]

Hypoglycaemia

In the SAVOR trial, the overall incidence of reported hypoglycaemia (recorded in daily patient diaries) was 17.1% in ONGLYZA-treated patients and 14.8% in placebo-treated patients.

The percent of subjects with reported on-treatment events of major hypoglycaemia (defined as an event that required assistance of another person) was higher in the saxagliptin group than in the placebo group (2.1% and 1.6%, respectively).

The increased risk of overall hypoglycaemia and major hypoglycaemia observed in the saxagliptin-treated group occurred primarily in subjects treated with a sulfonylurea at baseline and not in subjects on insulin or metformin monotherapy at baseline.

The increased risk of overall and major hypoglycaemia was primarily observed in subjects with HbA1c <7% at baseline.

Adverse Reactions related to ONGLYZA in Studies of Glycaemic control

There were 4148 patients with type 2 diabetes randomised, including 3021 patients treated with ONGLYZA, in six, double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of ONGLYZA on glycaemic control.

In a pre-specified pooled analysis of two monotherapy studies, the add-on to metformin study, the add-on to TZD study, and the add-on to glibenclamide study, the overall incidence of adverse events in patients treated with ONGLYZA 5 mg was similar to placebo. In the 24-week short-term period, discontinuation of therapy due to adverse events occurred in 3.3% and 1.8% of patients receiving ONGLYZA 5 mg and placebo, respectively. In the 24-week short-term combined with the long-term extension period, discontinuation of therapy due to adverse events occurred in 6.7% and 4.6% of patients receiving ONGLYZA 5 mg and placebo, respectively.

The adverse reactions in this short-term pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg and more commonly than in patients treated with placebo are shown in the following table.

Table 1 Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

	Number (%) of Patients	
	ONGLYZA 5 mg N=882	**Placebo N=799**
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

* The 5 placebo-controlled studies include two monotherapy studies and one add-on combination therapy study with each of the following: metformin, thiazolidinedione, or glibenclamide

In this pooled analysis, less common adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to placebo included the following: sinusitis, gastroenteritis, and vomiting, URI and UTI.

Adverse events of uncertain causality that were reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to placebo include hypertension, abdominal pain, rash, blood creatine phosphokinase increased, hypertriglyceridaemia, anaemia, depression, and anxiety.

A grouping of hypersensitivity-related events in the 5-study pooled analysis up to Week 24 showed an incidence of 1.5% and 0.4% in patients who received ONGLYZA 5 mg (all non-serious) and placebo, respectively.

Adverse Reactions Associated with ONGLYZA and Metformin as Initial Concomitant Therapy

In a 24-week, active-controlled study of initial therapy of ONGLYZA in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients are shown in Table 2.

Table 2 Initial Therapy with Combination of ONGLYZA and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and Greater Than in Patients Treated with Saxagliptin 10 mg Alone and Metformin Alone)

	Number (%) of Patients		
	ONGLYZA 5 mg + Metformin* N=320	**Saxagliptin 10 mg N=335**	**Metformin* N=328**
Headache	24 (7.5)	21 (6.3)	17 (5.2)
Nasopharyngitis	22 (6.9)	14 (4.2)	13 (4.0)

* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

In the 24 week phase of the ONGLYZA in combination with metformin as initial therapy study, less common adverse events reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to saxagliptin monotherapy and metformin included the following: bronchitis, dyspepsia, and back pain.

Adverse reactions reported in ≥2% of patients treated with ONGLYZA 5 mg plus metformin and ≥1% more frequently compared to saxagliptin 10 mg alone and metformin alone were in the combined short-term and long-term extension period were: nasopharyngitis and headache.

Peripheral Oedema

In the add-on to TZD study, the incidence of peripheral oedema was higher for ONGLYZA 5 mg plus TZD versus placebo plus TZD (8.1% versus 4.3%). In the combined short-term and long-term extension period, the incidence of peripheral oedema was higher for ONGLYZA 5 mg plus TZD versus placebo plus TZD (13.4% versus 9.8%). In a pooled analysis of the two monotherapy studies, the add-on to metformin study and the add-on to SU study (short-term 24 week), the overall incidence of adverse reactions of peripheral oedema observed in patients treated with ONGLYZA 5 mg alone or in combination was similar to placebo (1.7% versus 2.4%). In the SAVOR study, the

overall incidence of adverse reactions of peripheral oedema observed in patients treated with saxagliptin was similar to those treated with placebo (3.9% versus 4% respectively).

Hypoglycaemia

Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. Confirmed hypoglycaemia was defined as symptomatic hypoglycaemia with a fingerstick glucose value of ≤2.8 mmol/L.

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to TZD study (short-term 24 week), the overall incidence of adverse reactions of hypoglycaemia in patients treated with ONGLYZA 5 mg was similar to placebo (4.8% versus 4.3%).

In the 24-week study of initial therapy of ONGLYZA in combination with metformin, the incidence of hypoglycaemia was 3.4% in patients given ONGLYZA 5 mg plus metformin, 1.5% in patients given saxagliptin 10 mg alone, and 4.0% in patients given metformin alone. In the combined short-term and long-term extension period, the incidence of hypoglycaemia was 4.4% in patients given ONGLYZA 5 mg plus metformin, 1.8% in patients given saxagliptin 10 mg alone, and 5.2% in patients given metformin alone.

In the short-term 24-week add-on to glibenclamide study, the overall incidence of hypoglycaemia was higher for ONGLYZA 5 mg plus glibenclamide versus placebo plus up-titrated glibenclamide. The difference (14.6% versus 10.1%) was not statistically significant. The incidence of confirmed hypoglycaemia was 0.8% for ONGLYZA 5 mg plus glibenclamide and 0.7% for placebo plus up-titrated glibenclamide. In the combined short-term and long-term extension period of the add-on to glibenclamide study, the overall incidence of hypoglycaemia was 18.2% for ONGLYZA 5 mg and 12.0% for up-titrated glibenclamide; the incidence of confirmed hypoglycaemia was 1.6% for ONGLYZA 5 mg and 1.9% for up-titrated glibenclamide.

In the add-on to combination with metformin plus SU study, the overall incidence of hypoglycaemia experienced was 10.1 % for ONGLYZA 5 mg and 6.3% for placebo. Confirmed hypoglycaemia was reported in 1.6% of the ONGLYZA treated patients and none of the placebo treated patients.

In the analysis of pooled safety data of 1169 patients from trials evaluating saxagliptin in combination with dapagliflozin, the overall incidence of hypoglycaemia for the pooled safety data of was low (≤1.8% in any treatment group); there was no increase in hypoglycaemia in saxagliptin plus dapagliflozin plus metformin treatment group compared to the saxagliptin plus metformin or dapagliflozin plus metformin treatment groups. The combined use of saxagliptin plus dapagliflozin plus metformin was not associated with an increase in the risk of hypoglycaemia when compared to the individual agents as monotherapy. This was consistent with prior clinical trial experience regardless of whether the combination was added to metformin concurrently or sequentially.

In the add-on to insulin study, the overall incidence of reported hypoglycaemia was 18.4% for ONGLYZA 5 mg and 19.9% for placebo.

Vital signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA 5 mg.

Laboratory Tests

Across clinical studies, the incidence of laboratory adverse events was similar in patients treated with ONGLYZA 5 mg alone or in combination compared to patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte

count of approximately 2.2 x 10^9 c/L, a mean decrease of approximately 0.1 x 10^9 c/L relative to placebo was observed in a pooled analysis of five placebo-controlled clinical studies. Mean absolute lymphocyte counts remained stable and within the normal limits with daily dosing up to 102 weeks in duration. In the short-term period, the proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 1.5% and 0.4% in the saxagliptin 5 mg and placebo groups, respectively. In the short-term combined with long-term extension period of the pooled studies, the proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 1.6% and 1.0% in the saxagliptin 5 mg and placebo groups, respectively. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The clinical significance of this decrease in lymphocyte count relative to placebo is not known.

In the SAVOR trial, decreased lymphocyte counts were reported in 0.5% of ONGLYZA-treated patients and 0.4% of placebo-treated patients.

Postmarketing experience

During postmarketing experience the following adverse reactions have been reported with use of saxagliptin: acute pancreatitis, arthralgia, bullous pemphigoid and hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency. (*See Sections 4.3 Contraindications* and *4.4 Special warnings and precautions for use*.)

Reporting of suspected adverse reactions

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 www.tga.gov.au/reporting-problems

4.9 Overdose

Once-daily, orally-administered ONGLYZA has been shown to be safe and well-tolerated, with no clinically meaningful effect on QTc interval or heart rate at doses up to 400 mg daily for two weeks (80 times the recommended human dose of 5 mg/day).

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite are removed by hemodialysis (23% of dose over four hours).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Saxagliptin is a member of a class of oral anti-hyperglycaemic agents called DPP-4 inhibitors. Saxagliptin is a reversible, competitive, DPP-4 inhibitor with nanomolar potency. Saxagliptin demonstrates selectivity for DPP-4 versus other DPP enzymes, with greater than 75 fold selectivity over DPP-8 and DPP-9. Saxagliptin has extended binding to the DPP-4 active site, prolonging its inhibition of DPP-4. Saxagliptin exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of these active intact incretin hormones are increased by saxagliptin, thereby increasing and prolonging the actions of

these hormones. Saxagliptin also inhibits the cleavage of other substrates *in vitro*, but the relevance or consequences of DPP4 inhibition for these substrates in patients is unknown.

Incretin hormones are released by the intestine throughout the day and concentrations are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are elevated GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

Concentrations of GLP-1 are reduced in patients with type 2 diabetes, but saxagliptin increases active GLP-1 and GIP, potentiating these mechanisms. By increasing and prolonging active incretin concentrations, saxagliptin increases insulin release and decreases glucagon concentrations in the circulation in a glucose-dependent manner.

ONGLYZA improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through improvements in alpha and beta cell function as reflected by the actions described below.

Fasting glucose-dependent insulin secretion: ONGLYZA increases pancreatic beta-cell responsiveness to glucose in the fasting state and leads to enhanced insulin secretion and glucose disposal in the presence of elevated glucose concentrations.

Postprandial glucose-dependent insulin secretion: ONGLYZA increases pancreatic beta-cell responsiveness to glucose in the postprandial state and leads to enhanced postprandial insulin secretion and glucose disposal.

Postprandial glucagon secretion: In type 2 diabetes, paradoxical increases in glucagon secretion from alpha cells following meals stimulate hepatic glucose production and contribute to glycaemic dysregulation. ONGLYZA moderates glucagon secretion and lowers postprandial glucagon concentrations.

Pharmacodynamics

Improvement in Glycaemic Control

In patients with type 2 diabetes, administration of ONGLYZA led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C-peptide concentrations. The rise in insulin and the decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

In a clinical trial designed to study the effect of ONGLYZA on QTc interval, dosing with ONGLYZA was not associated with clinically meaningful prolongation of QTc interval or heart rate at daily doses up to 40 mg (8 times the Recommended Human Dose (RHD) of 5 mg/day). In a randomised, double-blind, placebo-controlled, four-way crossover, active comparator study, 40 healthy subjects were administered doses of saxagliptin up to 40 mg, placebo once daily for four days, or a single dose of moxifloxacin 400 mg as a positive control. Following the 40 mg dose, the maximum increase in the placebo-corrected mean changes in QTc interval and heart rate from baseline were 2.4 msec at 24 hours post-dose and 4.5 beats per minute at 4 hours post-dose, respectively.

Clinical trials

Improved Glycaemic Control

ONGLYZA has been studied as monotherapy and in combination with metformin; glibenclamide; and the thiazolidinediones, pioglitazone and rosiglitazone, an SGLT2 inhibitor and insulin. ONGLYZA has been studied with antidiabetic medicinal products as described below.

ONGLYZA should be used as part of combination treatment with other diabetic agents. Results from long-term studies of ONGLYZA on overall morbidity and mortality outcomes are not available.

There were 4148 patients with type 2 diabetes randomised, including 3021 patients treated with ONGLYZA, in six double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of ONGLYZA on glycaemic control. In these studies, the mean age of patients was 54 years, and 71% of patients were white, 16% were Asian, 4% were black, and 9% were of other racial groups. Mean duration of diabetes ranged from 1.7 years to 6.9 years, mean weight ranged from 76 kg to 90 kg, and mean BMI ranged from 29 to 32 mg/kg^2. An additional 423 patients, including 315 who received ONGLYZA, participated in a placebo-controlled, dose-ranging study of six to twelve weeks in duration.

In these six double-blind studies, ONGLYZA was evaluated at doses of 2.5 mg, 5 mg, and 10 mg once daily. Treatment with ONGLYZA at all doses produced clinically relevant and statistically significant improvements in haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG), including 2-hour PPG following standard oral glucose tolerance test (OGTT), compared to control. Reductions in HbA1c were seen across subgroups including gender, age, race, and baseline BMI. Overall, the 10 mg daily dose of saxagliptin did not provide greater efficacy than the 5 mg daily dose. The ONGLYZA 5 mg daily dose generally provided greater reductions in HbA1c and PPG compared to the ONGLYZA 2.5 mg daily dose.

ONGLYZA has been evaluated in six additional studies in patients with type 2 diabetes: an active-controlled study versus glipizide in 858 patients inadequately controlled on metformin alone, a placebo-controlled study with insulin in 455 type 2 diabetes patients inadequately controlled on a basal insulin (or insulin pre-mix) or a basal insulin (or insulin pre-mix) in combination with metformin; a placebo-controlled study in patients with type 2 diabetes, in 257 patients inadequately controlled on metformin plus a sulfonylurea, a placebo controlled study in 315 patients inadequately controlled on metformin and dapagliflozin, an active controlled study in combination with dapagliflozin in 534 patients inadequately controlled on metformin alone, and a placebo-controlled study in 170 patients with inadequate glycaemic control and renal impairment (moderate, severe or ESRD).

Combination Therapy

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this randomised, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycaemic control (HbA1c $\geq$7% and $\leq$10%) on metformin alone. Patients were required to be on a stable dose of metformin (1500 mg to 2550 mg daily) for at least 8 weeks to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, two-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily, for the duration of the study. Following the lead-in period, eligible patients were randomised to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin. Patients who failed to meet specific glycaemic goals during the study were

treated with pioglitazone rescue therapy, added on to placebo or ONGLYZA plus metformin. Dose titrations of ONGLYZA and metformin were not allowed in this study.

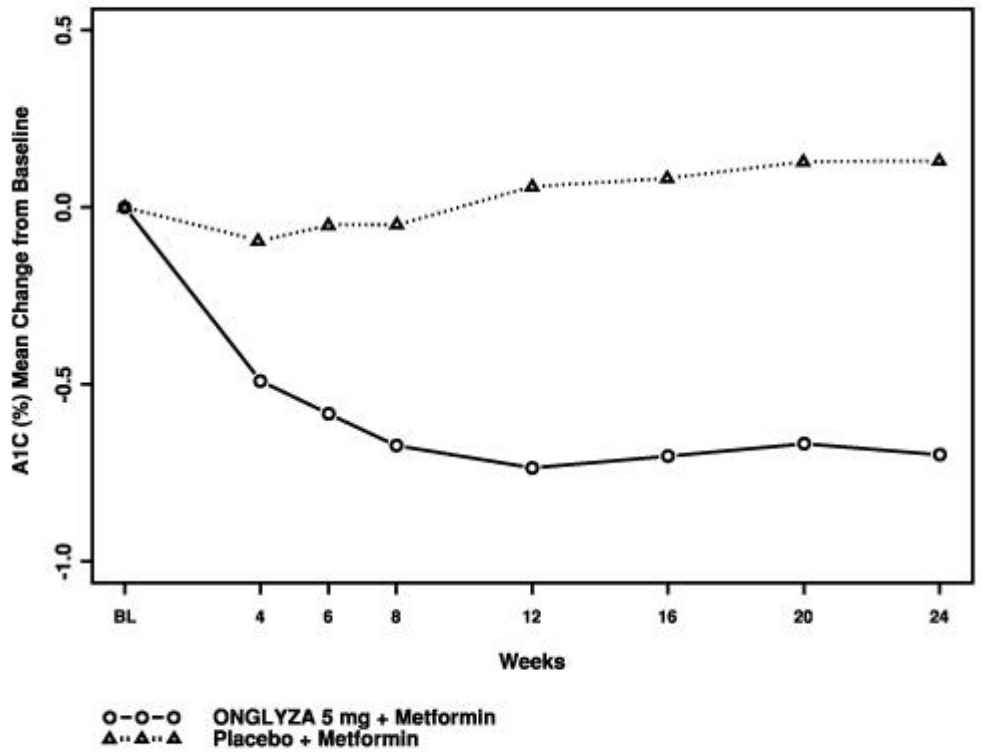
In combination with metformin, ONGLYZA 5 mg provided significant improvements in HbA1c, FPG, and PPG compared with the placebo plus metformin group (Table 3). Reductions in HbA1c at Week 4 (Figure 1) and FPG at Week 2 were seen in the ONGLYZA 5 mg plus metformin treatment groups relative to the placebo plus metformin group, the earliest time-points of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus metformin treatment groups compared with the placebo plus metformin group. Significant reductions in 2-hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus metformin treatment group (-3.2 mmol/L) compared with the placebo plus metformin group (-1.0 mmol/L). The proportion of patients who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria was higher in the placebo plus metformin group (27%) than in the ONGLYZA 5 mg plus metformin group (13%). Higher baseline HbA1c was associated with a greater adjusted mean change from baseline in HbA1c with ONGLYZA 5 mg plus metformin. The effect of ONGLYZA plus metformin on lipid endpoints in this study was similar to placebo. Similar reductions in body weight were observed in patients who received ONGLYZA plus metformin and placebo therapy (-0.9 kg and -0.9 kg, respectively).

Table 3 Glycaemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in combination with Metformin*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin**	**Placebo + Metformin**
HbA1c (%)	**N=186**	**N=175**
Baseline (mean)	8.1	8.1
Change from baseline (adjusted mean†)	−0.7	0.1
Difference from placebo (adjusted mean†)	−0.8‡	
95% Confidence Interval	(−1.0, −0.6)	
Percent of patients achieving HbA1c <7%	44%‡ (81/186)	17% (29/175)
FPG (mmol/L)	**N=187**	**N=176**
Baseline (mean)	9.9	9.7
Change from baseline (adjusted mean†)	−1.2	0.1
Difference from placebo (adjusted mean†)	−1.3‡	
95% Confidence Interval	(−1.7, −0.9)	
3-hour PPG AUC (mmol•min/L)	**N=146**	**N=131**
Baseline (mean)	2721	2631
Change from baseline (adjusted mean†)	−532	−183
Difference from placebo (adjusted mean†)	−349‡	
95% Confidence Interval	(−478, −221)	

* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. † Least squares mean adjusted for baseline value. ‡ p-value <0.0001 compared to placebo + metformin

Figure 1 Mean Change from Baseline in HbA1c in a Placebo-Controlled Study of ONGYLZA in Combination with Metformin*



* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. Mean change from baseline (LOCF).

Controlled Long-Term Study Extension

Of the patients that started the 24-week treatment, 162 (84.8%) and 149 (83.2%) patients who were taking ONGLYZA 5 mg plus metformin and placebo plus metformin respectively entered a controlled double blind long-term study extension. Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. Treatment with ONGLYZA 5 mg plus metformin was associated with a greater reduction in HbA1c than in the placebo plus metformin group, and the effect relative to placebo was sustained Week 102. The HbA1c change for ONGLYZA 5 mg plus metformin compared with placebo plus metformin was -0.8% at Week 102.

Add-On Combination Therapy with a Sulfonylurea

A total of 768 patients with type 2 diabetes participated in this randomised, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA in combination with sulfonylurea (SU) in patients with inadequate glycaemic control at enrollment (HbA1c ≥7.5% to ≤10%) on a submaximal dose of SU alone. Patients were required to be on a submaximal dose of SU for 2 months or greater to be enrolled in this study. In this study, ONGLYZA in combination with a fixed, intermediate dose of SU was compared to titration to a higher dose of SU.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period and placed on glibenclamide 7.5 mg once daily. Following the lead-in period, eligible patients with HbA1c ≥7% to ≤10% were randomised to either 2.5 mg or 5 mg of ONGLYZA plus 7.5 mg glibenclamide or placebo plus a 10 mg total daily dose of glibenclamide. Patients who received placebo were eligible to have glibenclamide up-titrated to a total daily dose of 15 mg. Up titration of glibenclamide was not allowed in patients who received ONGLYZA 2.5 or 5 mg. Glibenclamide could be down-titrated in any treatment group once during the 24-week study period due to hypoglycaemia as deemed necessary by the investigator. Approximately 92% of patients in the placebo plus glibenclamide group were up-titrated to a final total daily dose of 15 mg during the study period. Patients who failed to meet specific glycaemic goals during the study were treated with metformin rescue, added on to the ONGLYZA plus glibenclamide or the placebo plus up-titrated glibenclamide group. Dose titration of ONGLYZA was not permitted during the study.

In combination with glibenclamide, ONGLYZA 5 mg provided significant improvements in HbA1c, FPG, and PPG compared with the placebo plus up-titrated glibenclamide group (Table 4). Reductions in HbA1c (Figure 2) at Week 4 and FPG at Week 2 were seen in the ONGLYZA 5 mg plus glibenclamide treatment group relative to the placebo plus up-titrated glibenclamide group, the earliest timepoints of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus glibenclamide treatment group compared with the placebo plus up-titrated glibenclamide group. Significant reductions in 2 hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus glibenclamide treatment group (-1.9 mmol/L) compared with the placebo plus up-titrated glibenclamide (0.4 mmol/L). The proportion of patients who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria was higher in the placebo plus up-titrated glibenclamide group (30%) than in the ONGLYZA 5 mg plus glibenclamide group (17%). Higher baseline HbA1c was associated with a greater adjusted mean change from baseline in HbA1c with ONGLYZA 5 mg plus glibenclamide. The effect of ONGLYZA plus glibenclamide on lipid endpoints in this study was similar to placebo. In this study, small increases in body weight were seen in patients treated with ONGLYZA 5 mg plus glibenclamide and with placebo plus up-titrated glibenclamide (0.8 kg versus 0.3 kg, p=0.012).

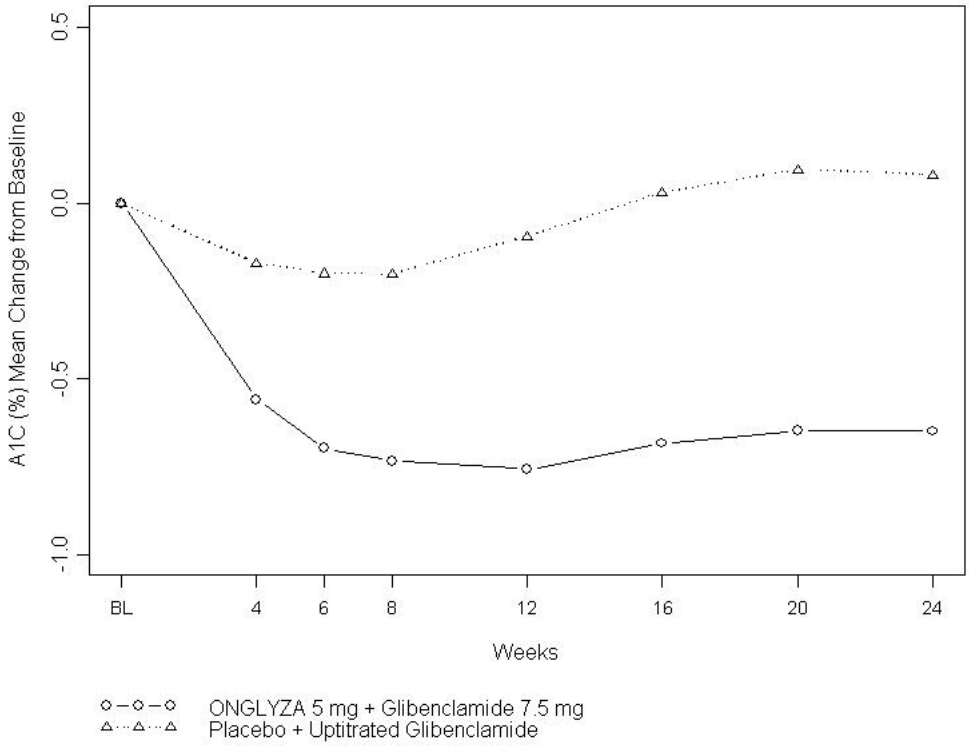
Table 4 Glycaemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in Combination with Glibenclamide*

Efficacy Parameter	**ONGLYZA 5 mg + Glibenclamide 7.5 mg**	**Placebo + Up-Titrated Glibenclamide**
HbA1c (%)	**N=250**	**N=264**
Baseline (mean)	8.5	8.4
Change from baseline (adjusted mean†)	−0.6	0.1
Difference from placebo (adjusted mean†)	−0.7‡	
95% Confidence Interval	(−0.9, −0.6)	
Percent of patients achieving HbA1c <7%	23%‡ (57/250)	9% (24/264)
FPG (mmol/L)	**N=252**	**N=265**
Baseline (mean)	9.7	9.7
Change from baseline (adjusted mean†)	−0.6	0.1
Difference from placebo (adjusted mean†)	−0.6§	
95% Confidence Interval	(−0.9, −0.2)	

Efficacy Parameter	ONGLYZA 5 mg + Glibenclamide 7.5 mg	Placebo + Up-Titrated Glibenclamide
3-hour PPG AUC (mmol•min/L)	**N=195**	**N=204**
Baseline (mean)	2794	2875
Change from baseline (adjusted mean†)	−278	66
Difference from placebo (adjusted mean†)	−344‡	
95% Confidence Interval	(−433, −254)	

* Intent-to-treat population using last observation on study prior to metformin rescue therapy. † Least squares mean adjusted for baseline value. ‡ p-value <0.0001 compared to placebo + up-titrated glibenclamide. § p-value=0.0020 compared to placebo + up-titrated glibenclamide

Figure 2 Mean Change from Baseline in HbA1c in a Placebo-Controlled Study of ONGLYZA in Combination with Glibenclamide*



* Intent-to-treat population using last observation on study prior to metformin rescue therapy. Mean change from baseline (LOCF).

Controlled Long-Term Study Extension

Of the patients that started the 24-week treatment, 227 (89.7%) and 235 (88%) patients who were taking ONGLYZA 5 mg plus glibenclamide and placebo plus up-titrated glibenclamide respectively entered a controlled double blind long-term study extension. Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. The HbA1c change for ONGLYZA 5 mg plus compared with placebo plus up-titrated glibenclamide was -0.7% at Week 76.

Add on combination therapy with a Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor

Concomitant initiation of saxagliptin and dapagliflozin in patients inadequately controlled on metformin

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycemic control on metformin alone (HbA1c≥8% and ≤12%) participated in this 24-week randomized, double blind, active comparator-controlled superiority trial with the combination of saxagliptin and dapagliflozin added concurrently to metformin, versus saxagliptin (DPP4 inhibitor) or dapagliflozin (SGLT2 inhibitor) added to metformin. Patients were randomized to one of three double-blind treatment groups to receive saxagliptin 5 mg and dapagliflozin 10 mg added to metformin XR, saxagliptin 5 mg and placebo added to metformin XR, or dapagliflozin 10 mg and placebo added to metformin XR. The saxagliptin and dapagliflozin combination group achieved significantly greater reductions in HbA1c versus either saxagliptin group or dapagliflozin group at 24 weeks (see Table 5).

Table 5 HbA1c at Week 24 (LRM[a]) in Active-Controlled Study Comparing the Combination of Saxagliptin and Dapagliflozin Added Concurrently to Metformin with either Saxagliptin or Dapagliflozin Added to Metformin

Efficacy Parameter	Saxagliptin 5 mg + Dapagliflozin 10 mg + Metformin N=179[b]	Saxagliptin 5 mg + Metformin N=176[b]	Dapagliflozin 10 mg + Metformin N=179[b]
HbA1c (%) at week 24[a]			
Baseline (mean)	8.9	9.0	8.9
Change from baseline (adjusted mean) (95% CI)	−1.5 (−1.6, −1.3)	−0.9 (−1.0, −0.7)	−1.2 (−1.4, −1.0)
Difference from saxagliptin+metformin (adjusted mean[c]) (95% CI)	−	0.6[d] (−0.8, −0.4-	-
Difference from dapagliflozin+metformin (adjusted mean[c]) (95% CI)		-	−0.3[e] (−0.5, −0.1)
Subjects (%) achieving HbA1C <7% (LOCF[f])			
Adjusted for baseline	41.4	18.3	22.2

[a] LRM = Longitudinal repeated measures (using values prior to rescue).

[b] Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[c] Least squares mean adjusted for baseline value.

[d] p-value < 0.0001.

[e] p-value=0.0166

Add-on therapy with saxagliptin in patients inadequately controlled on dapagliflozin plus metformin

In a 24-week randomised, double-blind, placebo-controlled study comparing the sequential addition of saxagliptin 5 mg to dapagliflozin 10 mg and metformin to placebo added to dapagliflozin 10 mg (SGLT2 inhibitor) and metformin in subjects with T2DM, the group with saxagliptin sequentially added to dapagliflozin and metformin achieved statistically significant (p-value <0.0001) greater reductions in HbA1c versus the placebo group at 24 weeks (see Table 6).

Table 6 HbA1c change from baseline at Week 24 (excluding data after rescue) for randomised subjects in studies assessing sequential addition of saxagliptin to a background of dapagliflozin and metformin

Efficacy parameter	Saxagliptin 5 mg added to Dapa 10 mg+Met (N=153)[a]	Placebo added to Dapa 10 mg+Met (N=162)[a]
HbA1c (%) at Week 24*		
Baseline (mean)	7.95	7.85
Change from baseline (adjusted mean[b]) (95% CI)	−0.51 (−0.63, −0.39)	−0.16 (−0.28, −0.04)
Comparison of saxa added to dapa+met vs.placebo+saxa+met - adjusted mean[b] (95% CI)	−0.35 (−0.52, −0.18) p-value <0.0001	
Subjects (%) achieving HbA1c < 7% Adjusted for baseline	35.3	23.1

* LRM = Longitudinal repeated measures (using values prior to rescue).

a Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

b Least squares mean adjusted for baseline value.

saxa= saxagliptin; dapa=dapagliflozin; met=metformin

Add on Combination Therapy with a Thiazolidinedione (TZD)

A total of 565 patients with type 2 diabetes participated in this randomised, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA in combination with a TZD (pioglitazone or rosiglitazone) in patients with inadequate glycaemic control (HbA1c ≥7% to ≤10.5%) on TZD alone. Patients were required to be on a stable dose of pioglitazone (30 mg to 45 mg once daily) or rosiglitazone (4 mg once daily or 8 mg either once daily or in two divided doses of 4 mg) for at least 12 weeks to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, two-week, dietary and exercise placebo lead-in period during which patients received TZD at their pre-study dose for the duration of the study. Following the lead-in period, eligible patients were randomised to 2.5 mg or 5 mg of ONGLYZA or placebo in addition to their current dose of TZD. Patients who failed to meet specific glycaemic goals during the study were treated with metformin rescue, added on to placebo or ONGLYZA plus TZD. Dose titration of ONGLYZA or TZD was not permitted during the study. A change in TZD regimen from rosiglitazone to pioglitazone at specified, equivalent therapeutic doses was permitted at the investigator's discretion if believed to be medically appropriate.

In combination with TZD, ONGLYZA 5 mg provided significant improvements in HbA1c, FPG, and PPG compared with the placebo plus TZD treatment group (Table 7). Reductions in HbA1c (Figure 3) at Week 4 and FPG at Week 2 were seen in the ONGLYZA 5 mg plus TZD treatment group relative to the placebo plus TZD group, the earliest timepoints of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus TZD treatment group compared with the placebo plus TZD group. Significant reductions in 2-hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus TZD treatment group (-3.6 mmol/L) compared with the placebo plus TZD group (-0.8 mmol/L). The proportion of patients who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria was 10% in the placebo plus TZD group and 6% for the 5 mg ONGLYZA plus TZD group. Higher baseline HbA1c was associated with a greater adjusted mean change from baseline in HbA1c with ONGLYZA 5 mg plus TZD. The effect of ONGLYZA plus TZD on lipid endpoints in this study

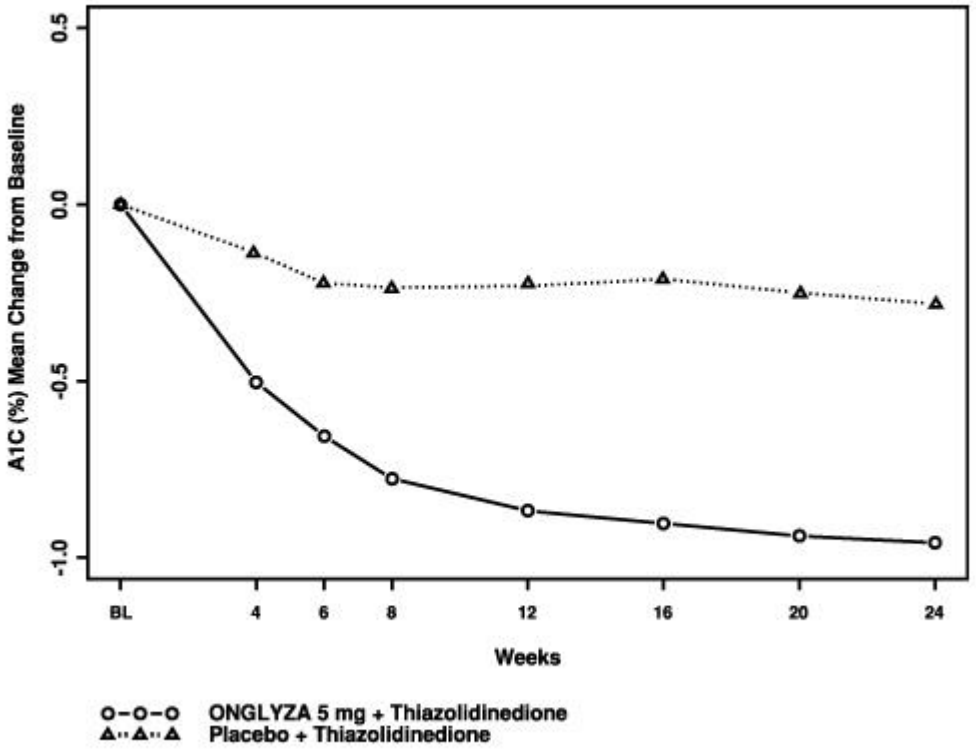
was similar to placebo. Small increases in body weight were observed in the ONGLYZA 5 mg plus TZD and placebo treatment groups (1.4 kg and 0.9 kg, respectively.)

Table 7 Glycaemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in Combination with a Thiazolidinedione*

Efficacy Parameter	**ONGLYZA 5 mg + TZD**	**Placebo + TZD**
HbA1c (%)	**N=183**	**N=180**
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean†)	−0.9	−0.3
Difference from placebo (adjusted mean†)	−0.6‡	
95% Confidence Interval	(−0.8, −0.4)	
Percent of patients achieving HbA1c <7%	42%§ (77/184)	26% (46/180)
FPG (mmol/L)	**N=185**	**N=181**
Baseline (mean)	8.9	9.0
Change from baseline (adjusted mean†)	−0.9	−0.2
Difference from placebo (adjusted mean†)	−0.8‖	
95% Confidence Interval	(−1.3, −0.3)	
3-hour PPG AUC (mmol•min/L)	**N=131**	**N=123**
Baseline (mean)	2657	2623
Change from baseline (adjusted mean†)	−514	−149
Difference from placebo (adjusted mean†)	−365‡	
95% Confidence Interval	(−490, −240)	

* Intent-to-treat population using last observation on study prior to metformin rescue therapy. † Least squares mean adjusted for baseline value. ‡ p-value <0.0001 compared to placebo + TZD. § p-value=0.0013 compared to placebo + TZD ‖ p-value=0.0005 compared to placebo + TZD

Figure 3 Mean Change from Baseline in HbA1c in a Placebo-Controlled Study of ONGLYZA in Combination with a Thiazolidinedione*



* Intent-to-treat population using last observation on study prior to metformin rescue therapy. Mean change from baseline (LOCF).

Controlled Long-Term Study Extension

Of the patients that started the 24-week treatment, 150 (80.6%) and 145 (78.8%) patients who were taking ONGLYZA 5 mg plus TZD and placebo plus TZD respectively entered a controlled double blind long-term study extension. Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. The HbA1c change for ONGLYZA 5 mg plus TZD compared with placebo plus TZD was –0.9% at Week 76.

Add-on combination therapy with metformin versus glipizide add-on combination therapy with metformin

A total of 858 patients with type 2 diabetes participated in this 52-week, randomised, double blind, active-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin compared with sulfonylurea in combination with metformin in patients with inadequate glycaemic control (HbA1c >6.5% and ≤10%) on metformin alone. Patients were required to be on a stable dose of metformin (at least 1500 mg daily) for at least 8 weeks to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin (1500-3000 mg based on their pre-study dose) for the duration of the study. Following the lead-in period, eligible patients were randomised to 5 mg of ONGLYZA or 5 mg of glipizide in addition to their current dose of open-label metformin. Patients in the glipizide plus metformin group had their glipizide dose titrated to

optimal effect (FPG ≤6.1 mmol/L) or the highest tolerable dose during the first 18 weeks using a double-dummy technique to a maximum of 20 mg per day. The mean dose of SU achieved in the study was 15 mg.

ONGLYZA 5 mg added to metformin was non-inferior to glipizide added to metformin in lowering HbA1c as per the primary analysis of the per protocol analysis set (Table 8). The intent-to-treat analysis showed consistent results.

ONGLYZA 5 mg resulted in a significantly lower proportion of patients with hypoglycaemic events, 3% (19 events in 13 patients) versus 36.3% (750 events in 156 patients) for glipizide.

Patients treated with ONGLYZA exhibited a significant reduction from baseline in body weight compared to a weight gain in patients administered glipizide (-1.1 kg versus +1.1 kg, p<0.0001).

Table 8 HbA1c at Week 52 in an Active-Controlled Trial of ONGLYZA in Combination with Metformin*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin**	**Glipizide + Metformin**
HbA1c (%)	N=293	N=293
Baseline (mean)	7.5	7.5
Change from baseline (adjusted mean†)	−0.7	−0.8
Difference vs glipizide + metformin (adjusted mean†)	−0.1	
95% Confidence Interval	(−0.1, −0.2) ‡	

* Per protocol population. † Least squares mean adjusted for baseline value. ‡ Saxagliptin + metformin is considered non-inferior to glipizide + metformin if the upper confidence limit of the estimate is <0.35%

Controlled long-term study extension

Patients who completed the initial 52-week study period were eligible to enter a controlled 52-week long-term study extension. Patients maintained the same dose of ONGLYZA 5 mg or glipizide in the long-term extension. Changes in HbA1c values from baseline were -0.4% for ONGLYZA 5 mg (N=184) added to metformin and -0.3% for glipizide (N=160) added to metformin at Week 104.

Treatment with ONGLYZA 5 mg plus metformin resulted in a lower proportion of patients with hypoglycaemic events, 3.5% (24 events in 15 patients) versus 38.4% (896 events in 165 patients) for treatment with glipizide plus metformin. Treatment with ONGLYZA 5 mg plus metformin resulted in a reduction in mean body weight compared with baseline values (-1.5 kg) whereas treatment with glipizide plus metformin resulted in an increase in mean body weight compared with baseline values (+1.3 kg) at Week 104. The overall safety profile of ONGLYZA 5 mg versus glipizide in the long-term treatment period was consistent with that previously observed in the initial 52-week treatment period.

Combination Triple Oral Therapy

A total of 257 patients with type 2 diabetes participated in this randomised, double-blind, placebo-controlled trial of 24-week duration to evaluate the efficacy and safety of ONGLYZA in combination with metformin plus a sulfonylurea in patients with inadequate glycaemic control (HbA1c ≥7% and ≤10%). Patients were to be on a stable combined dose of metformin extended-release or immediate-release (at maximum tolerated dose with minimum dose for enrolment being

1500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrolment being ≥50% of the maximum recommended dose) for at least eight weeks prior to enrolment.

Patients who met eligibility criteria were enrolled in a 2-week enrolment period to allow assessment of inclusion/exclusion criteria. Following the 2-week enrolment period, eligible patients were randomised to either double-blind ONGLYZA (5 mg once daily) or double-blind matching placebo for 24 weeks. During the 24-week double-blind treatment period, subjects were to receive metformin and a sulfonylurea at the same constant dose ascertained during enrolment. Sulfonylurea dose could be down titrated once in the case of major hypoglycaemic event or recurring minor hypoglycaemic events. In the absence of hypoglycaemia titration (up or down) of study medication during the treatment period was prohibited. Sulfonylureas used by patients in the study were glibenclamide, gliclazide, glimepiride or glipizide.

In combination with metformin and a sulfonylurea, ONGLYZA provided significant improvements in HbA1c and PPG compared with placebo plus metformin and sulfonylurea (Table 9)

Table 9 Glycaemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin plus Sulfonylurea*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin plus Sulfonylurea N=129**	**Placebo + Metformin plus Sulfonylurea N=128**
HbA1c (%)	**N=127**	**N=127**
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.1
Difference from placebo (adjusted mean†)	−0.7‡	
95% Confidence Interval	(−0.9, −0.5)	
Percent of patients achieving HbA1c <7%	31%§ (39/127)	9% (12/127)
2-hour PPG (mmol/L)	**N=115**	**N=113**
Baseline (mean)	14.85	14.54
Change from baseline (adjusted mean†)	-0.65	0.28
Difference from placebo (adjusted mean†)	-0.93θ	
95% Confidence Interval	(-1.77, -.0.09)	
FPG (mmol/L)	**N=121**	**N=123**
Baseline (mean)	8.99	8.63
Change from baseline (adjusted mean†)	-0.29	0.15
Difference from placebo (adjusted mean†)	-0.44#	
95% Confidence Interval	(-0.94, 0.06)	

* Intent-to-treat population using last observation prior to discontinuation. † Least squares mean adjusted for baseline value. ‡ p-value <0.0001 compared to placebo + metformin + sulfonylurea. § significance not tested θ p-value=0.0301 compared to placebo + metformin + sulfonylurea # Not statistically significant

Combination with Metformin as Initial Therapy

A total of 1306 treatment-naïve patients with type 2 diabetes participated in this randomised, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA as initial combination therapy with metformin in patients with inadequate glycaemic control (HbA1c ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naïve to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, one-week, dietary and exercise placebo lead-in period. Patients were randomised to one of four treatment arms: ONGLYZA 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. ONGLYZA was dosed once daily. During Weeks 1 through 5, in the ONGLYZA 5 mg and the saxagliptin 10 mg plus metformin groups, and the metformin alone group, metformin was up-titrated based on FPG levels in 500 mg per day increments as tolerated to a maximum of 2000 mg per day. Patients who failed to meet specific glycaemic goals during the studies were treated with pioglitazone rescue as add-on therapy.

Initial therapy with the combination of ONGLYZA 5 mg plus metformin provided significant improvements in HbA1c, FPG, and PPG compared with metformin alone (Table 10). Reductions in HbA1c at Week 4 and FPG at Week 2 were seen in the ONGLYZA 5 mg plus metformin treatment group relative to metformin alone, the earliest timepoints of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus metformin treatment group compared with metformin alone. Significant reductions in 2-hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus metformin group (-7.7 mmol/L) compared with the metformin alone group (-5.4 mmol/L). Significant improvements in HbA1c, FPG, and PPG were also seen in the ONGLYZA 5 mg plus metformin group compared with the saxagliptin alone group. Higher baseline HbA1c was associated with greater adjusted mean change from baseline in HbA1c in all treatment groups. Similar effects on lipid parameters were observed in all treatment groups. Similar reductions in body weight were seen in the ONGLYZA 5 mg plus metformin and in the metformin alone groups (-1.8 kg and -1.6 kg, respectively) with a smaller reduction seen in the saxagliptin 10 mg group.

Table 10 Glycaemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in Combination with Metformin as Initial Therapy and Metformin Alone*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin**	**Metformin**
HbA1c (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	−2.5	−2.0
Difference from placebo (adjusted mean†)	−0.5‡	
95% Confidence Interval	(−0.7,−0.4)	
Percent of patients achieving HbA1c <7%	60%‡ (185/307)	41% (129/314)
FPG (mmol/L)	**N=315**	**N=320**
Baseline (mean)	11.0	11.0
Change from baseline (adjusted mean†)	−3.3	−2.6
Difference from placebo (adjusted mean†)	−0.7§	
95% Confidence Interval	(−1.1,−0.3)	
3-hour PPG AUC (mmol•min/L)	**N=142**	**N=135**
Baseline (mean)	3082	3216
Change from baseline (adjusted mean†)	−1170	−833
Difference from placebo (adjusted mean†)	−337‡	
95% Confidence Interval	(−468,−207)	

* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. † Least squares mean adjusted for baseline value. ‡ p-value <0.0001 compared to metformin. § p-value=0.0002 compared to metformin

Controlled Long-Term Study Extension

Of the patients that started the 24-week treatment, 276 (86.3%) and 266 (81.1%) patients who were taking ONGLYZA 5 mg plus metformin and metformin respectively entered a controlled long-term study extension. Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. The HbA1c change for ONGLYZA 5 mg plus metformin compared with placebo plus metformin was –0.5% at Week 76.

Add-On Combination Therapy with Insulin (with or without metformin)

A total of 455 adult patients with type 2 diabetes participated in this randomised, double-blind, placebo-controlled trial of 24-week duration, to evaluate the efficacy and safety of ONGLYZA as add-on therapy to a basal insulin (or insulin pre-mix) in patients with inadequate glycaemic control (HbA1c ≥7.5% and ≤11%) on a basal insulin (or insulin pre-mix) alone (N=141) or on a basal insulin (or insulin pre-mix) in combination with a stable dose of metformin (N=314). Patients were required to be on a stable dose of insulin (≥30 units to ≤150 units daily) with ≤20% variation in total daily dose for ≥8 weeks prior to screening with or without metformin. Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise placebo lead-in period during which patients received insulin (and metformin if applicable) at their pre-study dose(s). Following the lead-in period, eligible patients were randomised to ONGLYZA 5 mg or placebo in addition to continuing their current dose of insulin (and metformin if applicable). Patients maintained a stable dose of insulin when possible. Patients who failed to meet specific glycaemic goals or who increased their insulin dose by >20% were rescued and subsequently switched (rescued) to a flexible insulin dose regimen (including increases in the dose of insulin and the addition of rapid acting or short-acting insulin, if needed). Dose titrations of ONGLYZA and metformin (if applicable) were not allowed in this study.

ONGLYZA 5 mg add-on to insulin with or without metformin provided significant improvements in HbA1c and PPG compared with placebo add-on to insulin with or without metformin (Table 11). Similar HbA1c reductions versus placebo were achieved for patients using ONGLYZA 5 mg add-on to insulin alone and ONGLYZA 5 mg add-on to insulin in combination with metformin (−0.4% and −0.4%, respectively). The proportion of patients who discontinued for lack of glycaemic control or who were rescued was 23% in the ONGLYZA 5 mg add-on to insulin group and 32% in the placebo add-on to insulin group.

Table 11 Glycaemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Insulin*

Efficacy Parameter	**ONGLYZA 5 mg + Insulin (±Metformin) N=304**	**Placebo + Insulin (±Metformin) N=151**
HbA1c (%)	**N=300**	**N=149**
Baseline (mean)	8.7	8.7
Change from baseline (adjusted mean[†])	−0.7	−0.3
Difference from placebo (adjusted mean[†])	−0.4[‡]	
95% Confidence Interval	(−0.6, −0.2)	
Percent of patients achieving HbA1c <7%	17%[§] (52/300)	7% (10/149)
FPG (mmol/L)	**N=262**	**N=129**
Baseline (mean)	9.6	9.6

Efficacy Parameter	ONGLYZA 5 mg + Insulin (±Metformin) N=304	Placebo + Insulin (±Metformin) N=151
Change from baseline (adjusted mean†)	−0.6	−0.3
Difference from placebo (adjusted mean†)	−0.2#	
95% Confidence Interval	(−0.7, 0.3)	
2-hour Postprandial Glucose (mmol/L)	**N=262**	**N=129**
Baseline (mean)	13.9	14.2
Change from baseline (adjusted mean†)	−1.5	−0.2
Difference from placebo (adjusted mean†)	−1.3¶	
95% Confidence Interval	(−2.1, −0.5)	
Mean Total Daily Dose of Insulin (unit)	**N=299**	**N=151**
Baseline (mean)	53	55
Change from baseline (adjusted mean†)	2	5
Difference from placebo (adjusted mean†)	−3§	
95% Confidence Interval	(−6,−1)	

* Intent-to-treat population using last observation on study prior to insulin rescue therapy for patients needing rescue. Mean Total Daily Dose of Insulin: Intent-to-Treat population using last observation on study † Least squares mean adjusted for baseline value and metformin use at baseline. ‡ p-value <0.0001 compared to placebo + insulin. § Significance not tested ¶ p-value = 0.0016 compared to placebo + insulin # Not statistically significant

In the above study, the overall incidence of reported hypoglycaemia was 18.4% and 19.9% for the ONGLYZA and placebo groups, respectively. No therapeutic interaction was seen with metformin in this study.

Controlled long-term study extension

Patients who completed all visits during the initial 24-week study period were eligible to enter a controlled long-term study extension. Patients who received ONGLYZA in the initial 24 week study period maintained the same dose of ONGLYZA in the long-term extension, but patients who completed the 24-week study period with a stable insulin dose were switched to a flexible insulin dose regimen for the extension period. All efficacy analyses were based on data regardless of insulin dose. Treatment with ONGLYZA 5 mg add-on to insulin with or without metformin was associated with a greater reduction in HbA1c than placebo add-on to insulin with or without metformin, and the effect relative to placebo was sustained to Week 52. The HbA1c change for ONGLYZA 5 mg plus insulin (N=244) compared with placebo plus insulin (N=124) was −0.4% at Week 52.

Patients with Renal Impairment

A total of 170 patients participated in a 12-week, randomised, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of saxagliptin 2.5 mg once daily compared with placebo in patients with type 2 diabetes and moderate (n=90) or severe (n=41) renal impairment or ESRD (n=39). In this study, 98.2% of the patients entered the study on and continued antihyperglycaemic medications (insulin and/or oral antihyperglycaemic drug) other than the study drug (75.3% on insulin and 31.2% on oral antihyperglycaemic drug; some received both).

Treatment with saxagliptin 2.5 mg provided significant improvement in HbA1c versus placebo (mean reduction from baseline at Week 12 of −0.9% for the saxagliptin group and −0.4% for the placebo group, p=0.007).

The safety profile of saxagliptin in this study was consistent with that previously observed in the clinical trial experience. There were no adverse effects on renal function. The number of subjects with any hypoglycaemic event was similar between the treatment groups.

Controlled long-term study extension

Patients who completed the initial 12-week study period were eligible to enter a controlled 40-week long-term study extension. Patients who received saxagliptin in the initial 12-week study period maintained the same dose of saxagliptin in the long-term extension. Most subjects (76%) in both treatment groups receiving insulin or other antihyperglycaemic medications had no change in dose or type of medication during the 52-week treatment period. In subjects who had a significant change in type or dose of insulin (more than +/− 20%) or OAD, efficacy data thereafter were excluded from the analysis.

Treatment with saxagliptin 2.5 mg provided sustained improvement in HbA1c versus placebo (mean reduction from baseline at Week 52 of −1.4% for the saxagliptin group and −0.5% for the placebo group).

The safety profile of saxagliptin in the long-term treatment period was consistent with that previously observed in the clinical trial experience and that observed in the short-term (12-week) treatment period of this study.

Elderly Patients

Of the 16,492 patients randomised in the SAVOR trial, 8561 (51.9%) patients were 65 years and over and 2330 (14.1%) were 75 years and over. The number of subjects treated with ONGLYZA in the SAVOR study that were 65 years and over was 4290 and the number of subjects that were 75 years and over was 1169.

Of the total number of subjects (N=4148, of which 3021 received ONGLYZA) in six, double-blind, controlled clinical safety and efficacy studies of ONGLYZA, 634 (15.3%) patients were 65 years and over, of which 59 (1.4%) patients were 75 years and over.

No overall differences in safety or effectiveness were observed between subjects 65 years and over, 75 years and over, and younger subjects.

Cardiovascular safety

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the effect of ONGLYZA (saxagliptin) on the occurrence of major cardiovascular disease (CVD) events was assessed in 16,492 adult patients with type 2 diabetes who had either established CVD or multiple risk factors for vascular disease. Patients were randomly assigned to placebo (n=8212) or saxagliptin (5 mg or 2.5 mg for patients with moderate or severe renal insufficiency) once daily (n=8280). The demographics and baseline characteristics of subjects were balanced between the saxagliptin and placebo groups (See Table 12). Subjects were followed for a mean duration of 2 (median=2.0) years.

Table 12 Demographic and Diabetes-Related Baseline Characteristics (SAVOR ITT population)

Parameter		**ONGLYZA (N=8280)**	**Placebo (N=8212)**
Gender, n (%)	Male Female	5512 (66.6) 2768 (33.4)	5525 (67.3) 2687 (32.7)
Age (years)[a]	Mean (min, max)	65.1 (39.0, 99.0)	65.0 (40.0, 93.0)

Parameter		ONGLYZA (N=8280)	Placebo (N=8212)
Age group (years)[a], n (%)	≥65	4290 (51.8)	4271 (52.0)
	≥75	1169 (14.1)	1161 (14.1)
Duration of T2DM (years)	Mean (min, max)	12.0 (0.0, 60.9)	11.9 (0.0, 60.7)
HbA1c (%), n (%)	≥7	6097 (73.6)	5983 (72.9)
eGFR category (mL/min)[b], n (%)	>50	6986 (84.4)	6930 (84.4)
	≥30 to ≤ 50	1122 (13.6)	1118 (13.6)
	<30	172 (2.1)	164 (2.0)
CV risk Subjects with MRF[c], n (%) Subjects with established CVD[d], n (%)		 1789(21.6) 6494 (78.4)	 1747 (21.3) 6465 (78.7)
Baseline diabetes medication, n (%)	Metformin	5765 (69.6)	5658 (68.9)
	Insulin	3423 (41.3)	3364 (41.0)
	Sulfonylurea	3327 (40.2)	3259 (39.7)
	Thiazolidinedione	510 (6.2)	460 (5.6)
Baseline CVD medication, n (%)	ACE inhibitor/ARB	6478 (78.2)	6517 (79.4)
	Statin	6482 (78.3)	6435 (78.4)
	Aspirin	6249 (75.5)	6155 (75.0)
	Beta-blockers	5101 (61.6)	5061 (61.6)
	Non-aspirin anti-platelet medication	1986 (24.0)	1960 (23.9)

a – At randomisation; b – estimated GFR using MDRD formula, calculated as 175 x standardised serum creatinine$^{-1.154}$ x age$^{-0.203}$ x 1.212 (if black) x 0.742 (if female); c - Subjects with Multiple Risk Factors (MRF) for vascular disease without a previous CV event; d - Subjects with history of CV event(s).

Concomitant medication use was similar for the two treatment groups and was managed throughout the trial to local guideline targets for glycaemic control and CV risk reduction in order to minimise differences between the two treatment groups.

The primary safety and efficacy endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following major adverse CV events (MACE): CV death, non-fatal myocardial infarction, or non-fatal ischaemic stroke. The primary and secondary end-points are described in Table 13.

Table 13 Primary and secondary SAVOR study objectives

Objective	Description
Primary efficacy	Determine, as a superiority assessment, whether treatment with saxagliptin, compared with placebo when added to current background therapy, resulted in a significant reduction in the primary MACE endpoint.
Primary safety	Establish that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite MACE endpoint observed with saxagliptin to that observed in the placebo group is less than 1.3
Secondary efficacy	Determine whether treatment with saxagliptin compared with placebo when added to current background therapy in subjects with T2DM will result in a reduction of the composite MACE endpoint plus hospitalisation for heart failure, hospitalisation for unstable angina pectoris, or hospitalisation for coronary revascularisation.
Secondary efficacy	Determine whether treatment with saxagliptin compared with placebo when added to current background therapy in subjects with T2DM would result in a reduction of all-cause mortality

Saxagliptin did not increase the CV risk (CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke) in patients with T2DM compared to placebo when added to current background therapy (HR 1.00; 95% CI: 0.89, 1.12; P<0.001 for non-inferiority). No increased risk for the primary endpoint was observed between saxagliptin and placebo in any of the following subgroups: CVD, multiple risk factors for CVD, mild, moderate, or severe renal impairment, age, gender, race, region, duration of type 2 diabetes, history of heart failure, baseline HbA1c, albumin/creatinine ratio, baseline anti-diabetic medication, or baseline use of statins, aspirin, ACE inhibitors, ARBs, beta-blockers, or anti-platelet medications.

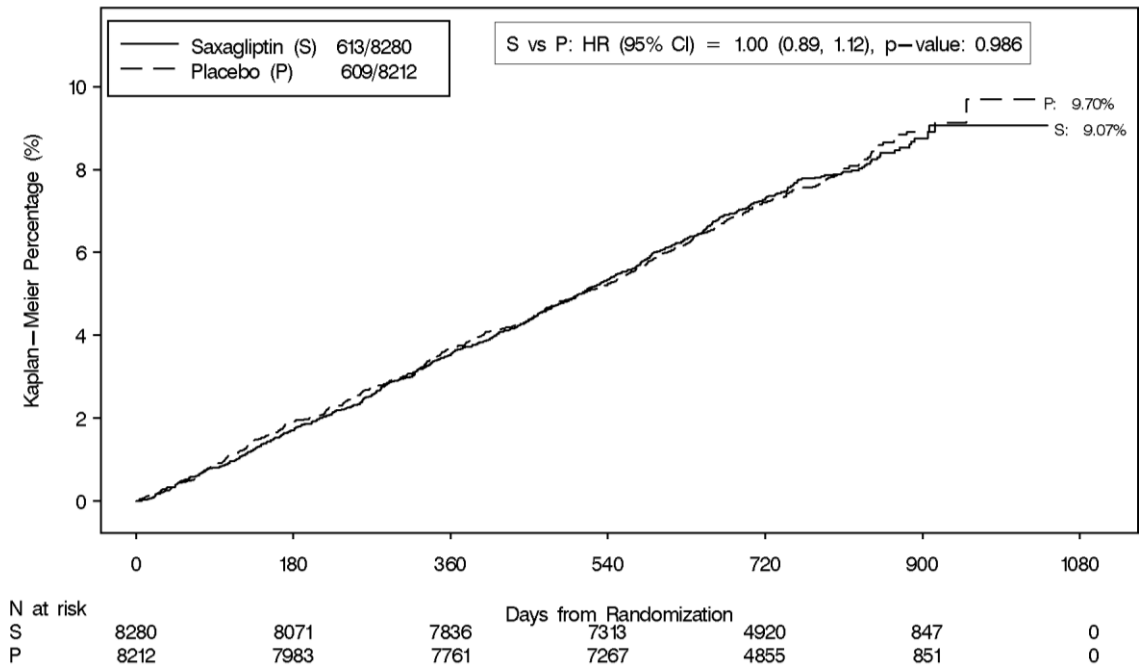
The primary efficacy endpoint did not demonstrate a statistically significant difference in major adverse coronary events for saxagliptin compared to placebo when added to current background therapy in patients with T2DM.

Table 14 Primary and Secondary Clinical Endpoints by Treatment Group in the SAVOR study*

Endpoint	ONGLYZA (N=8280)		Placebo (N=8212)		Hazard Ratio (95% CI)†
	Subjects with events n (%)	Event rate per 100 patient-yrs	Subjects with events n (%)	Event rate per 100 patient-yrs	
Primary composite endpoint: MACE	613 (7.4)	3.76	609 (7.4)	3.77	1.00 (0.89,1.12)‡,§
Secondary composite endpoint: MACE plus	1059 (12.8)	6.72	1034 (12.6)	6.60	1.02 (0.94,1.11)#
All-cause mortality	420 (5.1)	2.50	378 (4.6)	2.26	1.11 (0.96, 1.27)#

* Intent-to-treat population. † Hazard ratio adjusted for baseline renal function category and baseline CVD risk category ‡ p-value <0.001 for non-inferiority (based on HR<1.3) compared to placebo. § p-value = 0.99 for superiority (based on HR<1.0) compared to placebo + insulin #Significance not tested.

Figure 4 Cumulative percent of time to first CV event for primary composite endpoint*



* Intent-to-treat population

One component of the secondary composite endpoint, hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance (ie, without adjustment for testing of multiple endpoints) favouring placebo [HR = 1.27; (95% CI 1.07, 1.51); P = 0.007]. Clinically relevant factors predictive of increased relative risk with saxagliptin treatment could not be definitively identified. Subjects at higher risk for hospitalisation for heart failure, irrespective of treatment assignment, could be identified by known risk factors for heart failure such as baseline history of heart failure or impaired renal function. However, subjects on saxagliptin with a history of heart failure or impaired renal function at baseline were not at an increased risk relative to placebo for the primary or secondary composite endpoints or all-cause mortality.

Additional endpoints in the SAVOR trial included assessment of the parameters used measure glycaemic control and whether treatment with saxagliptin compared with placebo would result in a reduction in the need for increase in dose or addition of new antidiabetic medication. Despite active management of concomitant anti-diabetic therapy in both study arms, mean HbA1c levels were lower in the saxagliptin group compared to the placebo group at Year 1 (7.6% versus 7.9%, difference of -0.35% [95%CI: -0.38, -0.31]) and at Year 2 (7.6% versus 7.9%, difference of -0.30% [95% CI: -0.34, -0.26]). The proportions of subjects with HbA1c <7% in the saxagliptin group compared to the placebo group were 38% versus 27% at Year 1 and 38% versus 29% at Year 2.

Compared to placebo, saxagliptin resulted in less need for the initiation of new or increases in current oral diabetes medications or insulin. The improvements in HbA1c and the proportion of subjects reaching HbA1c targets among saxagliptin-treated subjects were observed despite lower rates of upward adjustments in diabetes medications or initiation of new diabetes medications or insulin compared with placebo.

5.2 Pharmacokinetic properties

The pharmacokinetics of saxagliptin has been extensively characterised in healthy subjects and patients with type 2 diabetes. Saxagliptin was rapidly absorbed after oral administration, with maximum saxagliptin plasma concentrations (C_{max}) usually attained within two hours after administration in the fasted state. The C_{max} and AUC values increased proportionally to the increment in the saxagliptin dose. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma $AUC_{(INF)}$ values for saxagliptin and its major metabolite were 78 ng·h/mL and 214 ng·h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The intra-subject coefficients of variation for saxagliptin C_{max} and AUC were less than 12%.

Following a single oral dose of 5 mg saxagliptin to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin was 2.5 hours, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of ONGLYZA is due to high potency, high affinity, and extended binding to the active site. No appreciable accumulation was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg.

Results from population-based exposure modelling indicate that the pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Absorption

Based on food effects studies, ONGLYZA may be administered with or without food. However, in pivotal efficacy and safety studies ONGLYZA was generally taken prior to the morning meal. The amount of saxagliptin absorbed following an oral dose is at least 75%. The absolute oral bioavailability of saxagliptin is approximately 50% (90% CI of 48-53%). Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with a high-fat meal resulted in no change in saxagliptin C_{max} and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach C_{max} (T_{max}) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

Distribution

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is below measurable levels. Thus, changes in blood protein levels in various disease states (eg, renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Metabolism

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin. It also demonstrates selectivity for DPP-4 versus other DPP enzymes, with greater than 163 fold selectivity over DPP-8 and DPP-9.

Excretion

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its major metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. For the major metabolite, renal clearance values were

comparable to estimated glomerular filtration rate. A total of 22% of the administered radioactivity was recovered in faeces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract.

Pharmacokinetics of the Major Metabolite

The C_{max} and AUC values for the major metabolite of saxagliptin increased proportionally to the increment in the saxagliptin dose. Following single oral doses of 2.5 mg to 400 mg saxagliptin in the fed or fasted states, the mean AUC values for the major metabolite ranged from 2-7 times higher than the parent saxagliptin exposures on a molar basis. Following a single oral dose of 5 mg saxagliptin in the fasted state, the mean terminal half-life ($t_{1/2}$) value for the major metabolite was 3.1 hours and no appreciable accumulation was observed upon repeated once-daily dosing at any dose.

Special Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with End Stage Renal Disease (ESRD) on haemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

Males: $\text{CrCl (mL/min)} = \dfrac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 1.2}{[\text{serum creatinine (micromol/L)}]}$

Females: 0.85 × value calculated using formula for males

The degree of renal impairment did not affect the C_{max} of saxagliptin or its major metabolite. In subjects with CrCL>50 mL/min (approximately corresponding to eGFR ≥45 mL/min/1.73 m^2 by Modified Diet in Renal Disease [MDRD] eGFR equation, following post-hoc re-analysis) the AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than AUC values in subjects with normal renal function. Increases of this magnitude are not clinically relevant, therefore dosage adjustment in these patients is not recommended. In subjects with renal impairment with CrCL≤50 mL/min (approximately corresponding to eGFR <45 mL/min/1.73 m^2, following post-hoc re-analysis) or in subjects with ESRD on haemodialysis, the AUC values of saxagliptin and its major metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. In patients with eGFR <45 mL/min/1.73 m^2 the dose recommended is 2.5 mg once daily. Use of saxagliptin in patients with ESRD requiring haemodialysis is not recommended. *See Sections 4.2 Dose and method of administration – Special patient populations (Renal impairment) and 4.4 Special Warnings and Precautions for Use – Use in renal impairment).*

Hepatic Impairment

There were no clinically meaningful differences in pharmacokinetics for subjects with mild, moderate, or severe hepatic impairment; therefore, no dosage adjustment for ONGLYZA is recommended for patients with hepatic impairment. In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The corresponding C_{max} and AUC of the major metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful.

Elderly Patients

No dosage adjustment of ONGLYZA is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for parent saxagliptin than young subjects (18-40 years). Differences in major metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in parent saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the major metabolite in young and elderly subjects is likely to be due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its major metabolite in an exposure modelling analysis.

Paediatric and Adolescent

Pharmacokinetics in the paediatric population have not been studied.

Gender

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the major metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its major metabolite in an exposure modelling analysis.

Race

No dosage adjustment is recommended based on race. An exposure modelling analysis compared the pharmacokinetics of saxagliptin and its major metabolite in 309 white subjects with 105 non-white subjects (consisting of 6 racial groups). No significant difference in the pharmacokinetics of saxagliptin and its major metabolite were detected between these two populations.

Body Mass Index

No dosage adjustment is recommended based on body mass index (BMI). BMI was not identified as a significant covariate on the apparent clearance of saxagliptin or its major metabolite in an exposure modelling analysis.

5.3 Preclinical safety data

Genotoxicity

The mutagenic and clastogenic potential of saxagliptin was tested at high concentrations and exposures in a battery of genetic toxicity studies including an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo*/*in vitro* cytogenetics study in rat peripheral blood lymphocytes. Saxagliptin was not mutagenic or clastogenic based on the combined outcomes of these studies. The major metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

Carcinogenicity

Two-year carcinogenicity studies were conducted in mice and rats. Saxagliptin did not induce tumours in mice treated at up to 600 mg/kg/day, producing exposure 1123-times that of humans at the recommended clinical dose. In rats, no increase in tumours was observed in males treated with saxagliptin at up to 150 mg/kg/day and females at up to 300 mg/kg/day (relative exposure at the highest doses, approximately 400 and 2465, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, macrogol 3350, titanium dioxide, purified talc, iron oxide yellow CI77492 (2.5 mg tablet only), iron oxide red CI77491 (5 mg tablet only) and Opacode Blue (printing ink).

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 30°C.

6.5 Nature and contents of container

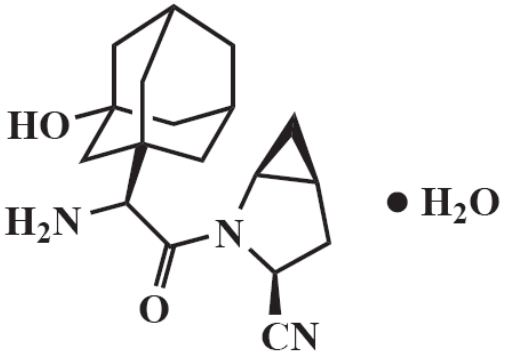
ONGLYZA is available in aluminium/ aluminium blister packs of 7 and 28 tablets.

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

Chemical structure



Saxagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferators-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

The chemical name of saxagliptin is (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxytricyclo [3.3.1.1^{3,7}] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate.

Molecular formula: C18H25N3O2•H2O

Molecular weight: 333.43 (monohydrate)

Saxagliptin is a white to light yellow or light brown powder. It is soluble in polyethylene glycol 400, acetone, acetonitrile, ethanol, isopropyl alcohol, methanol; sparingly soluble in water and slightly soluble in ethyl acetate.

CAS number

945667-22-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

18 March 2011

10 DATE OF REVISION

25 February 2019

Summary table of changes

Section changed	Summary of new information
Various	PI reformat
4.2	Renal Updates
4.4	Renal Updates Information on Use in Elderly Patients that pertains to Clinical Trials has been moved to section 5.1 Pharmacodynamics-Clinical Trials
5.2	Renal Updates

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