

Attachment 1: Product information for AusPAR Onglyza Saxagliptin (as hydrochloride) Bristol-Myers Squibb Australia Pty Ltd PM-2011-01174-3-5 Final 13 March 2013. This Product Information was approved at the time this AusPAR was published.

ONGLYZA[®]

saxagliptin

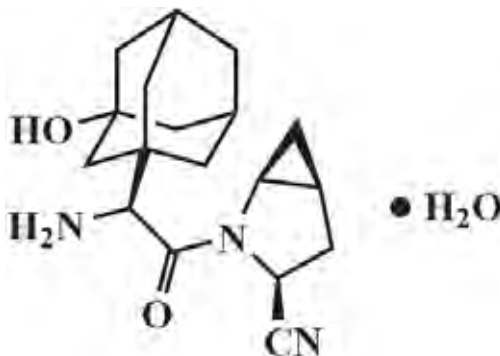
PRODUCT INFORMATION

NAME OF THE MEDICINE

ONGLYZA (saxagliptin) is an orally-active inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes mellitus. Saxagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferators-activated receptor gamma (PPAR γ) 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.

The chemical structure of saxagliptin is:



CAS number: 945667-22-1

Molecular formula: C₁₈H₂₅N₃O₂·H₂O

Molecular weight: 333.43 (monohydrate)

DESCRIPTION

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.

Each film-coated tablet of ONGLYZA contains 5 mg of saxagliptin free base (as saxagliptin hydrochloride) and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl

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alcohol, macrogol 3350, titanium dioxide, talc-purified, iron oxide red CI77491 (5 mg tablet only) and Opacode Blue (printing ink).

PHARMACOLOGY

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.

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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.

Pharmacokinetics

The pharmacokinetics of saxagliptin has been extensively characterized 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

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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 ¹⁴C-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:

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

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Females: $0.85 \times$ 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 mild renal impairment, 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 patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment 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. See Dosage and Administration.

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

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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.

Pharmacodynamics

General

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

ONGLYZA has been studied as monotherapy and in combination with metformin; glibenclamide; the thiazolidinediones, pioglitazone and rosiglitazone; and insulin. ONGLYZA has not been studied in triple oral combination therapy. ONGLYZA has been studied with antidiabetic medicinal products as described below.

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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/kg². 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 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.

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

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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 1). 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 1 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

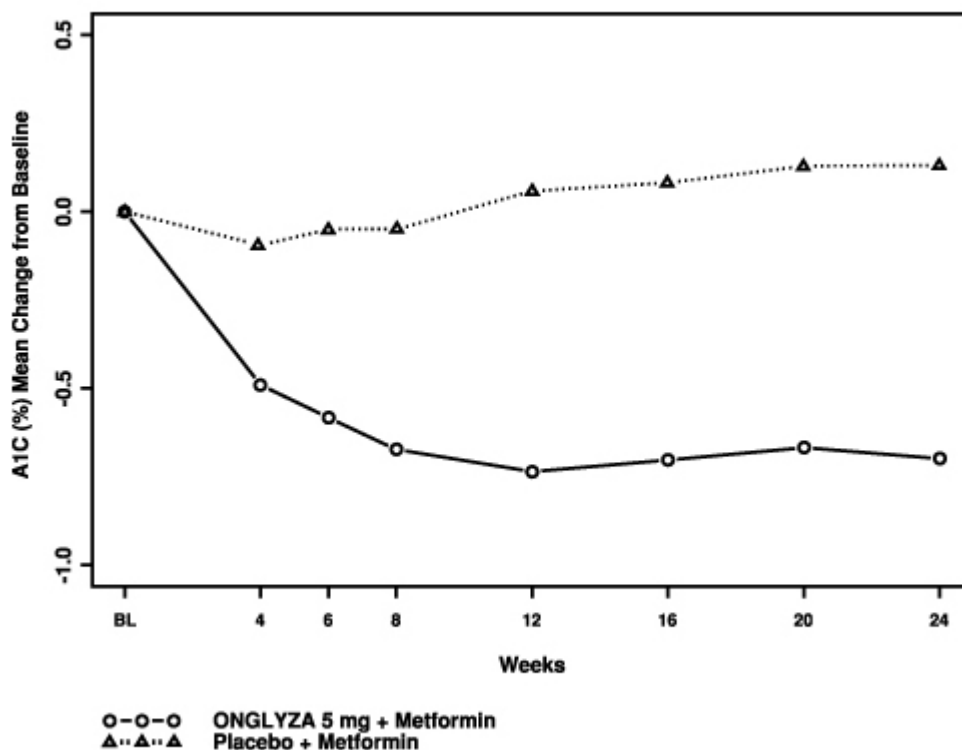
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Efficacy Parameter	ONGLYZA 5 mg + Metformin	Placebo + Metformin
Change from baseline (adjusted mean [†])	-532	-183
Difference from placebo (adjusted mean [†])	-349 [‡]	
95% Confidence Interval	(-478, -221)	

* 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

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Figure 1 Mean Change from Baseline in HbA1c in a Placebo-Controlled Study of ONGLYZA 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 at Week 50 and Week 102 compared to placebo. The HbA1c change for ONGLYZA 5 mg plus metformin (n=100 observed, n=187 LOCF) compared with placebo plus metformin (n=59 observed, n=175 LOCF) was -0.7% at Week 50. The HbA1c change for ONGLYZA 5 mg plus metformin (n=31 observed, n=184 LOCF) compared with placebo plus metformin (n=15 observed, n=172 LOCF) was -0.7% at Week 102.

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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 $\geq 7.5\%$ to $\leq 10\%$) 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 $\geq 7\%$ to $\leq 10\%$ 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 2). 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

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treated with ONGLYZA 5 mg plus glibenclamide and with placebo plus up-titrated glibenclamide (0.8 kg versus 0.3 kg, p=0.012).

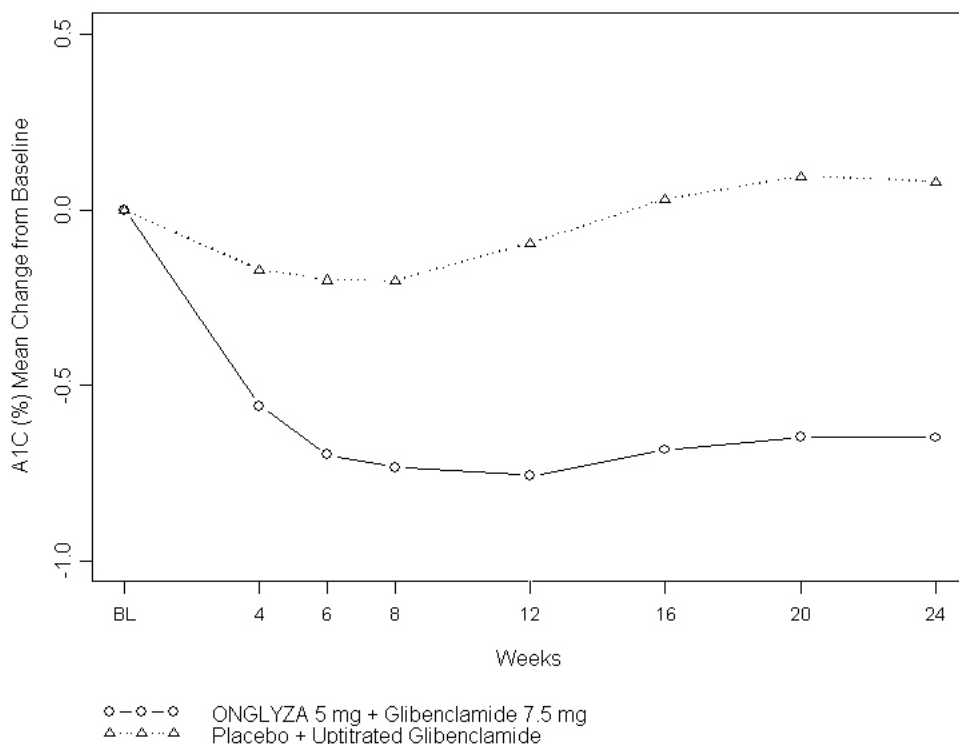
Table 2 Glycaemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in Combination with Glibenclamide*

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)	
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

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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 glibenclamide (n=99 observed, n=243 LOCF) compared with placebo plus up-titrated glibenclamide (n=61 observed, n=253 LOCF) was -0.6% at Week 50.

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 $\geq 7\%$ to $\leq 10.5\%$) on TZD alone. Patients were required to be on a stable dose of pioglitazone (30 mg to 45 mg

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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 3). 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 3 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 [‡]	

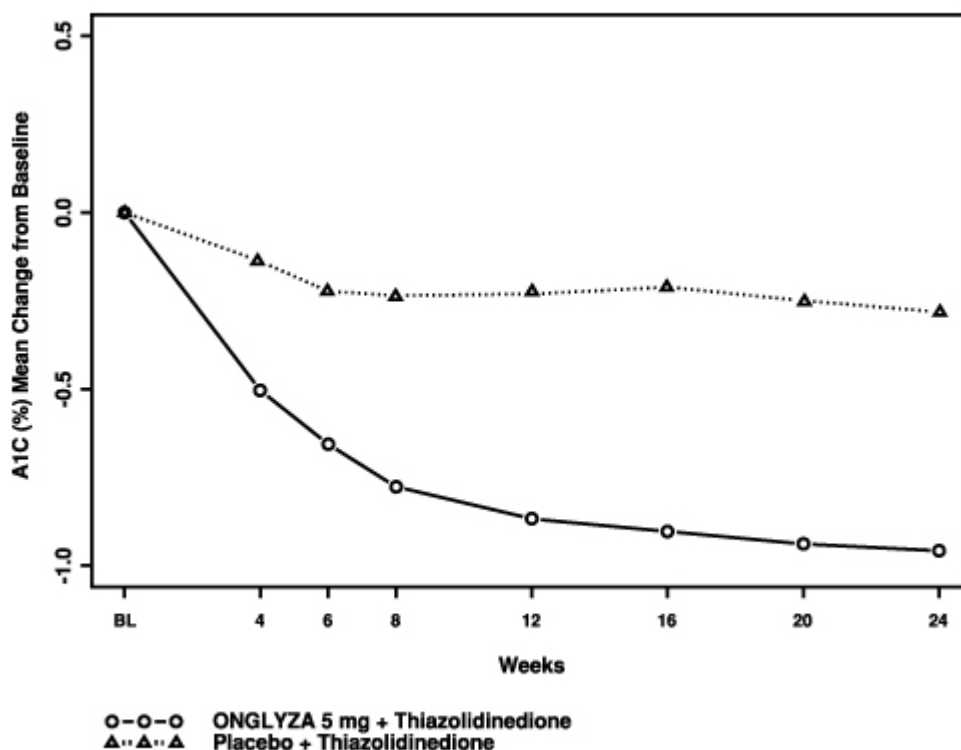
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Efficacy Parameter	ONGLYZA 5 mg + TZD	Placebo + TZD
95% Confidence Interval	(-0.8, -0.4)	
Percent of patients achieving HbA1c <7%	42% [§] (77/184)	26% (46/180)
FPG (mmol/L)	N=185	N=181
Baseline (mean)	8.9	9.0
Change from baseline (adjusted mean [†])	-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

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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 (n=65 observed, n=135 LOCF) compared with placebo plus TZD (n=48 observed, n=130 LOCF) was -0.7% at Week 50.

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 $\geq 8\%$ to $\leq 12\%$) on

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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 4). 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 4 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)	

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Efficacy Parameter	ONGLYZA 5 mg + Metformin	Metformin
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 (n=46 observed, n=100 LOCF) compared with placebo plus metformin (n=33 observed, n=91 LOCF) was -0.5% at Week 50 compared to placebo.

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.

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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 5). 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 5 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
	N=300	N=149
HbA1c (%)		
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
Change from baseline (adjusted mean [†])	−0.6	−0.3
Difference from placebo (adjusted mean [†])	−0.2 [#]	
95% Confidence Interval	(−0.7, 0.3)	

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Efficacy Parameter	ONGLYZA 5 mg + Insulin (±Metformin) N=304	Placebo + Insulin (±Metformin) N=151
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.

INDICATIONS

Add-on combination

ONGLYZA is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.

ONGLYZA is indicated in patients with type 2 diabetes mellitus to improve glycaemic control as add-on therapy to premixed or basal insulin (with or without metformin) when premixed or basal insulin (with or without metformin) used with diet and exercise, do not provide adequate glycaemic control. 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.

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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).

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.

PRECAUTIONS

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 Contraindications and Adverse effects.)

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 Adverse effects.)

Use in Patients with Renal Impairment

There is limited experience in patients with moderate or severe renal impairment and in patients with End Stage Renal Disease (ESRD) on haemodialysis. Therefore ONGLYZA should not be used in these patients. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. The recommended clinical dose is unchanged in patients with mild renal impairment. (See Dosage and Administration.) ONGLYZA should not be used in more significant degrees of renal impairment.

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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 Adverse Effects.)

Effects on ability to drive and to 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.

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.

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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.

Paediatric use

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

Use in elderly

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, and younger subjects. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. Experience in patients aged 75 years and older is very limited and caution should be exercised when treating this population.

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 Dosage and Administration)

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).

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

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combined outcomes of these studies. The major metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

Interactions with other medicines

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, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4. 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, as described below, 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 oral contraceptive.

Metformin

Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an hOCT-1 and hOCT-2 substrate, decreased the C_{max} of saxagliptin by 21%; however, the AUC was unchanged. Saxagliptin did not alter the pharmacokinetics of metformin. Therefore, ONGLYZA is not an inhibitor of hOCT-1 and hOCT-2-mediated transport and meaningful interactions with other hOCT-1 and hOCT-2 substrates would not be expected.

Glibenclamide

Coadministration of a single dose of saxagliptin (10 mg) and glibenclamide (5 mg), a CYP2C9 substrate, increased the C_{max} of saxagliptin by 8%; however, the AUC of saxagliptin was unchanged. The plasma C_{max} of glibenclamide increased by 16%; however, the AUC of glibenclamide was unchanged. Therefore, ONGLYZA

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does not meaningfully inhibit CYP2C9-mediated metabolism and meaningful interactions with other CYP2C9 substrates would not be expected.

Pioglitazone

Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of saxagliptin. The plasma C_{max} of pioglitazone increased by 14%; however, the AUC of pioglitazone was unchanged. Therefore, ONGLYZA does not meaningfully inhibit or induce CYP2C8-mediated metabolism and meaningful interactions with other CYP2C8 substrates would not be expected.

Digoxin

Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of saxagliptin or digoxin. Therefore, ONGLYZA is not an inhibitor or inducer of P-gp-mediated transport and meaningful interactions with other P-gp substrates would not be expected.

Simvastatin

Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, increased the C_{max} of saxagliptin by 21%; however, the AUC of saxagliptin was unchanged. Saxagliptin did not alter the pharmacokinetics of simvastatin. Therefore, ONGLYZA is not an inhibitor or inducer of CYP3A4/5-mediated metabolism and meaningful interactions would not be expected with other substrates of CYP3A4/5.

Diltiazem

Coadministration of a single dose of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the C_{max} of saxagliptin by 63% but the AUC for the total active components of saxagliptin by 21%. The plasma C_{max} of diltiazem increased by 16%; however, the AUC of diltiazem was unchanged. Therefore, ONGLYZA would not be expected to meaningfully alter the pharmacokinetics of moderate CYP3A4/5 inhibitors and meaningful interactions with other moderate CYP3A4/5 inhibitors would not be expected.

Ketoconazole

Coadministration of a single dose of saxagliptin (100 mg) and ketoconazole (200 mg every 12 hours at steady state), a potent inhibitor of CYP3A4/5 and P-gp, increased the C_{max} for saxagliptin by 62% but the AUC for the total active components of saxagliptin by 13%. The plasma C_{max} and AUC of ketoconazole decreased by 16 and 13% respectively. Therefore, ONGLYZA would not be expected to meaningfully alter the pharmacokinetics of potent CYP3A4/5 and P-gp inhibitors and meaningful interactions would not be expected with other potent CYP3A4/5 and P-gp inhibitors.

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Rifampicin

Coadministration of a single dose of saxagliptin (5 mg) and rifampicin (600 mg once daily to steady state), a potent inducer of CYP3A4/5 and P-gp, decreased the C_{max} for saxagliptin by 53% but the AUC for the total active components of saxagliptin by 26%. The plasma DPP4 activity inhibition by ONGLYZA over a dose interval (24 h) was not meaningfully affected by the coadministration of rifampicin.

Omeprazole

Coadministration of multiple once-daily doses of saxagliptin (10 mg) and omeprazole (40 mg), a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3, did not alter the pharmacokinetics of saxagliptin. Therefore, meaningful interactions of ONGLYZA with other CYP2C19 inhibitors or MRP-3 inducers would not be expected.

Aluminium hydroxide + magnesium hydroxide + simethicone

Coadministration of a single dose of saxagliptin (10 mg) and a liquid containing aluminium hydroxide (2400 mg), magnesium hydroxide (2400 mg), and simethicone (240 mg) decreased the C_{max} of saxagliptin by 26%; however, the AUC of saxagliptin was unchanged. Therefore, meaningful interactions of ONGLYZA with antacid and antigas formulations of this type would not be expected.

Famotidine

Administration of a single dose of saxagliptin (10 mg) three hours after a single dose of famotidine (40 mg), an inhibitor of hOCT-1, hOCT-2, and hOCT-3, increased the C_{max} of saxagliptin by 14%; however, the AUC of saxagliptin was unchanged. Therefore, meaningful interactions of ONGLYZA would not be expected with other inhibitors of hOCT-1, hOCT-2, and hOCT-3.

Oral Contraceptives

Coadministration of multiple once-daily doses of saxagliptin (5 mg) and a combined oral contraceptive (0.035 mg ethinyl estradiol/0.250 mg norgestimate), for 21 days, did not alter the steady state pharmacokinetics of the primary active estrogen component, ethinyl estradiol, or the primary active progestin component, norelgestromin. When saxagliptin was coadministered with 0.035 mg ethinyl estradiol/0.250 mg norgestimate, the plasma AUC of norgestrel, an active metabolite of norelgestromin, was increased by 13% and the plasma C_{max} of norgestrel was increased by 17%. This small magnitude change in AUC and C_{max} of norgestrel is not considered to be clinically meaningful. Based on these findings, saxagliptin would not be expected to meaningfully alter the pharmacokinetics of an estrogen/progestin combined oral contraceptive.

Other interactions

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

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

ADVERSE EFFECTS

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 $\geq 5\%$ of patients treated with ONGLYZA 5 mg and more commonly than in patients treated with placebo are shown in the following table.

Table 6 Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies* Reported in $\geq 5\%$ 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 $\geq 2\%$ of patients treated with ONGLYZA 5 mg and $\geq 1\%$ more frequently compared to placebo included the following: sinusitis, gastroenteritis, and vomiting.

In the combined short-term and long-term extension periods of the placebo controlled studies, adverse reactions reported in $\geq 2\%$ of patients treated with

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ONGLYZA 5 mg and $\geq 1\%$ more frequently compared to placebo were: upper respiratory tract infection, urinary tract infection and gastroenteritis. Adverse events of uncertain causality that were reported in $\geq 2\%$ of patients treated with ONGLYZA 5 mg and $\geq 1\%$ more frequently compared to placebo include: abdominal pain, rash, blood creatine phosphokinase increased, hypertriglyceridaemia, anaemia, depression, and anxiety.

In short-term combined with long-term periods of pooled studies, the incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

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 and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalisation or were reported to be life-threatening by the investigators.

Adverse Reactions Associated with ONGLYZA and Concomitant Therapy

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 in this study, defined as symptoms of hypoglycaemia accompanied by a fingerstick glucose value of ≤ 2.8 mmol/L, 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 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%). Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required.

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%).

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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 $\geq 5\%$ of patients are shown in Table 7. 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.

Table 7 Initial Therapy with Combination of ONGLYZA and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in $\geq 5\%$ 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 this study, less common adverse events that were reported in $\geq 2\%$ of patients treated with ONGLYZA 5 mg and $\geq 1\%$ more frequently compared to saxagliptin monotherapy and metformin included the following: bronchitis, dyspepsia, and back pain.

In the combined short-term and long-term extension period, adverse reactions in placebo controlled studies reported in $\geq 2\%$ of patients treated with ONGLYZA 5 mg and $\geq 1\%$ more frequently compared to saxagliptin 10 mg alone and metformin alone were: nasopharyngitis and headache. Hypertension, an adverse event of uncertain causality, was reported in $\geq 2\%$ of patients treated with ONGLYZA 5 mg and $\geq 1\%$ more frequently compared to placebo.

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.

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

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patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2.2×10^9 c/L, a mean decrease of approximately 0.1×10^9 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.

Postmarketing experience

During postmarketing experience the following adverse reactions have been reported with use of saxagliptin: acute pancreatitis 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 Contraindications and Precautions.)

DOSAGE AND ADMINISTRATION

ONGLYZA tablets must not be split or cut.

Add-On Combination Therapy

The recommended dose of ONGLYZA is 5 mg once daily as add-on combination therapy with metformin, a thiazolidinedione, or a sulfonylurea.

In patients with inadequate glycaemic control with premixed or basal insulin (with or without metformin), the recommended dose of ONGLYZA is 5mg once daily. 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 CLINICAL TRIALS).

ONGLYZA can be taken with or without food.

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

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have their metformin dose increased according to approved metformin Product Information.

Renal impairment

Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. Renal function can be estimated from serum creatinine using the Cockcroft-Gault formula or Modification of Diet in Renal Disease (MDRD) formula.

ONGLYZA should not be used in patients with moderate or severe renal impairment and in patients with End Stage Renal Disease (ESRD) on haemodialysis, due to limited experience in these patients. In patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min; estimated Glomerular Filtration Rate [eGFR] >50 mL/min/1.73m²), the recommended clinical dose is ONGLYZA 5 mg daily

Hepatic impairment

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

Paediatric and adolescent

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

Geriatric

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 Precautions)

OVERDOSAGE

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).

Contact the Poisons Information Centre for advice on management.

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PRESENTATION AND STORAGE CONDITIONS

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.

ONGLYZA is available in blister packs of 7 and 28 tablets. Store below 30°C.

NAME AND ADDRESS OF SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
ABN 33 004 333 322
4 Nexus Court,
Mulgrave, VIC 3170

Marketed in Australia by

Bristol-Myers Squibb Australia Pty Ltd
ABN 33 004 333 322
4 Nexus Court,
Mulgrave, VIC 3170

and

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF APPROVAL

Date of approval: 19 September 2012

DATE OF MOST RECENT AMENDMENT

1 November 2012

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