KOMBIGLYZE®

saxagliptin/metformin hydrochloride immediate release

PRODUCT INFORMATION

NAME OF THE MEDICINE

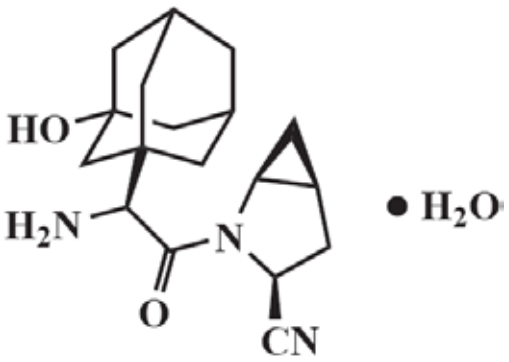
KOMBIGLYZE (saxagliptin/metformin hydrochloride) immediate release tablets contain two oral antihyperglycaemic drugs used in the management of type 2 diabetes: saxagliptin and metformin hydrochloride.

Saxagliptin

Saxagliptin is an orally-active inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme.

Saxagliptin is described chemically as (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

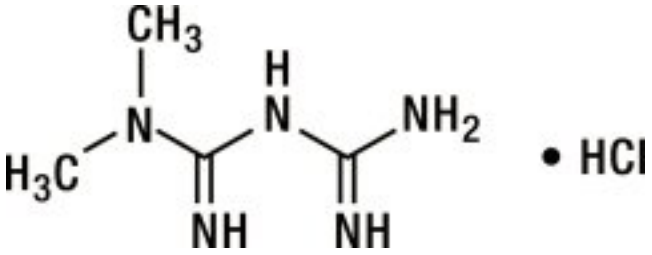
Molecular formula: $C_{18}H_{25}N_3O_2 \bullet H_2O$

Molecular weight: 333.43 (monohydrate)

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide with antihyperglycaemic effects.

The chemical structure of metformin hydrochloride is:



CAS number: 1115-70-4

Molecular formula: $C_4H_{11}N_5 \bullet HCl$

Molecular weight: 165.63

DESCRIPTION

Saxagliptin

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.

Metformin hydrochloride

Metformin hydrochloride is a white to off-white crystalline compound. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Kombiglyze

KOMBIGLYZE is available for oral administration as immediate release tablets containing the following active ingredients:

- 2.5 mg/500 mg strength: 2.5 mg saxagliptin (as saxagliptin hydrochloride) and 500 mg metformin hydrochloride
- 2.5 mg/850 mg strength: 2.5 mg saxagliptin (as saxagliptin hydrochloride) and 850 mg metformin hydrochloride
- 2.5 mg/1000 mg strength: 2.5 mg saxagliptin (as saxagliptin hydrochloride) and 1000 mg metformin hydrochloride

Each film-coated tablet of KOMBIGLYZE contains the following inactive ingredients: povidone, magnesium stearate, polyvinyl alcohol, macrogol 3350, titanium dioxide, purified talc, iron oxide red CI77491 (2.5 mg/500 mg and

2.5 mg/850 mg tablets), iron oxide yellow CI77492 (2.5 mg/850 mg and 2.5 mg/1000 mg tablets) and Opacode Blue (printing ink).

PHARMACOLOGY

Mechanism of Action

KOMBIGLYZE combines two anti-hyperglycaemic agents with complementary mechanisms of action to improve both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with type 2 diabetes: saxagliptin, a DPP4 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Saxagliptin

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 DPP-4 inhibition for these substrates in patients is unknown.

This glucose-dependent mechanism is unlike the mechanism seen with sulfonylureas, whereby insulin is released even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations.

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.

Saxagliptin 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: Saxagliptin 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: Saxagliptin 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. Saxagliptin moderates glucagon secretion and lowers postprandial glucagon concentrations.

Metformin hydrochloride

Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **Precautions**) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

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

Pharmacokinetics

The results of bioequivalence studies in healthy subjects demonstrated that the area under the curve (AUC) and maximum concentration (C_{max}) of both saxagliptin and metformin from the 2.5 mg/500 mg and 2.5 mg/1000 mg KOMBIGLYZE tablets are bioequivalent to the co-administration of corresponding doses of saxagliptin and metformin hydrochloride immediate-release administered as individual tablets. Based on these results and in vitro dissolution testing, the 2.5 mg/850 mg KOMBIGLYZE tablets are also considered to be equivalent to the co-administration of corresponding doses of saxagliptin and metformin hydrochloride immediate-release administered as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of KOMBIGLYZE.

Saxagliptin

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 Cmax 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 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

Saxagliptin

Based on food effects studies, saxagliptin may be administered with or without food. However, in pivotal efficacy and safety studies saxagliptin 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.

Metformin hydrochloride

After an oral dose of metformin, T_{max} is reached in 2.5 hours. The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin 500 to 1500 mg, and 850 to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an

alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Saxagliptin

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.

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time.

Metabolism

Saxagliptin

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.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Excretion

Saxagliptin

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.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Pharmacokinetics of the Major Metabolite

Saxagliptin

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 10 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

KOMBIGLYZE should not be used in patients with renal impairment (See **Contraindications** and **Precautions**.)

<u>Saxagliptin</u>

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 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.

Metformin hydrochloride

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

Hepatic Impairment

Saxagliptin

There were no clinically meaningful differences in pharmacokinetics for subjects with mild, moderate, or severe hepatic impairment; therefore, no dosage adjustment for saxagliptin 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.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Elderly Patients

Saxagliptin

No dosage adjustment of saxagliptin 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.

Metformin hydrochloride

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

Paediatric and Adolescent

Saxagliptin

Pharmacokinetics in the paediatric population have not been studied.

Gender

Saxagliptin

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.

Metformin hydrochloride

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

Race

Saxagliptin

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.

Metformin hydrochloride

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

Body Mass Index

Saxagliptin

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

Saxagliptin

In patients with type 2 diabetes, administration of saxagliptin 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.

Treatment with saxagliptin 5 mg and metformin extended-release administered once daily with the evening meal for 4 weeks produced significant reductions in average glucose concentration over the 24-hour dosing interval (defined as 24-hour glucose area under the curve divided by 24 hours) when compared to placebo plus metformin extended-release (mean placebo-corrected reduction of 0.9 mmol/L; P=0.0001) with consistent improvements in measured plasma glucose values throughout the 24-hour dosing interval. Significant reductions in 2-hour postprandial glucose and 2-day average fasting plasma glucose were seen (mean placebo corrected reductions of 2.0 mmol/L; P=0.0010 and 0.8 mmol/L; P=0.0002, respectively).

Cardiac Electrophysiology

Saxagliptin

In a clinical trial designed to study the effect of saxagliptin on QTc interval, dosing with saxagliptin 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

The coadministration of saxagliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on metformin alone, in treatment-naive patients inadequately controlled on diet and exercise alone, compared with sulfonylurea in combination with metformin in patients with inadequate glycaemic control on metformin alone, and studied in a subgroup of patients inadequately controlled on insulin plus metformin. Treatment with saxagliptin plus metformin at

all doses produced clinically relevant and statistically significant improvements in haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to placebo in combination with metformin (initial or add-on therapy). Reductions in HbA1c were seen across subgroups including gender, age, race, and baseline BMI.

In the initial combination and add-on to metformin studies, decrease in body weight in the treatment groups given saxagliptin in combination with metformin was similar to that in the groups given metformin alone. Saxagliptin plus metformin was not associated with significant changes from baseline in fasting serum lipids compared to metformin alone.

There have been no clinical efficacy studies conducted with KOMBIGLYZE; however, bioequivalence of KOMBIGLYZE with coadministered saxagliptin and metformin hydrochloride immediate release tablets was demonstrated.

Saxagliptin twice daily add on to metformin therapy

An add on to metformin placebo controlled study of 12 week duration was conducted in 160 patients to evaluate the efficacy and safety of saxagliptin 2.5 mg twice daily in combination with metformin in patients with inadequate glycaemic control (HbA1c ≥7.0% and ≤10.0% at randomisation) on metformin alone. Patients were required to be on a stable dose of at least 1500 mg metformin given twice daily. After 12 weeks, the saxagliptin 2.5 mg twice daily plus metformin group (n=74) had a significantly greater HbA1c mean reduction from baseline compared with the placebo plus metformin group (n=86) (0.56% vs. 0.22%, respectively, difference of 0.34%). Clinical trial experience of twice daily administration of saxagliptin is limited to this study and has not been directly compared to once daily dosing in clinical trials.

Addition of Saxagliptin to 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 saxagliptin in combination with metformin in patients with inadequate glycemic control (HbA1c ≥7% and ≤10%) on metformin alone. Patients were required to be on a stable dose of metformin (1500-2550 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 saxagliptin 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

saxagliptin plus metformin. Dose titrations of saxagliptin and metformin were not allowed in this study.

In combination with metformin, saxagliptin 5 mg provided significant improvements in HbA1c, FPG, and PPG compared with the placebo plus metformin group (Table1). Reductions in HbA1c at Week 4 (Figure 1) and FPG at Week 2 were seen in the saxagliptin 5 mg plus metformin treatment groups relative to the placebo plus metformin group, the earliest timepoints of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the saxagliptin 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 saxagliptin 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 saxagliptin 5 mg plus metformin group (13%). Higher baseline HbA1c was associated with a greater adjusted mean change from baseline in HbA1c with saxagliptin 5 mg. The effect of saxagliptin on lipid endpoints in this study was similar to placebo. Similar reductions in body weight were observed in patients who received saxagliptin and placebo therapy (−0.9 kg and −0.9 kg, respectively).

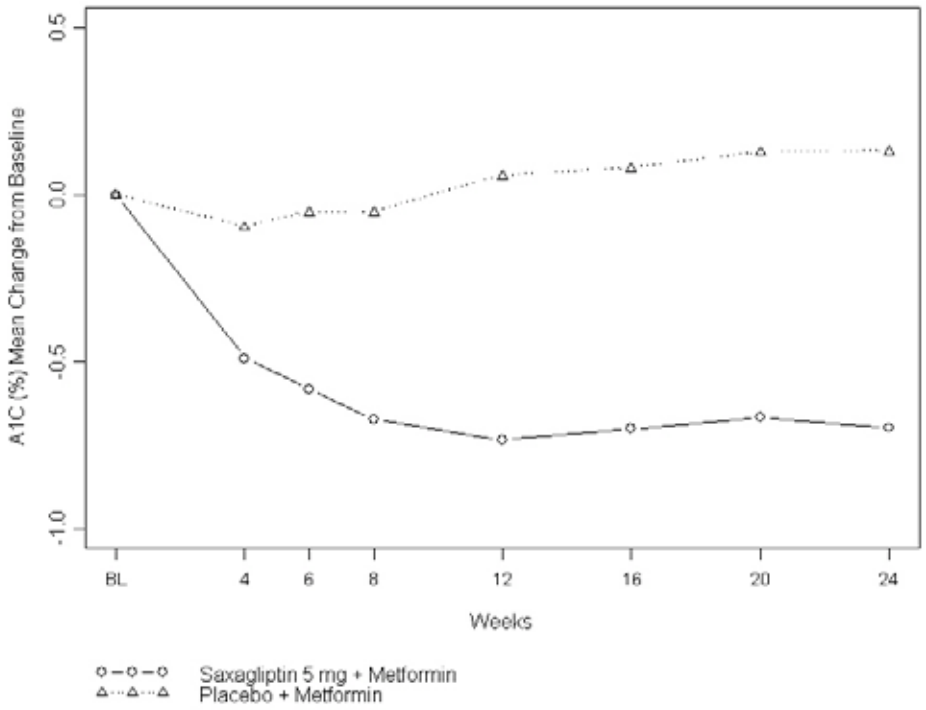
Table 1 Glycaemic Parameters at Week 24 in a Placebo-Controlled Study of Saxagliptin 5 mg in combination with Metformin*

Efficacy Parameter	**Saxagliptin 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

Efficacy Parameter	Saxagliptin 5 mg + Metformin	Placebo + Metformin
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 Saxagliptin 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 extension

Patients who were rescued (based on predefined glucose levels) during the initial 24-week study period as well as those who completed all visits during the initial 24-week study period without need for rescue therapy were eligible to enter a controlled long-term study extension. Patients who received saxagliptin in the initial 24-week study period maintained the same dose of saxagliptin in the long-term extension. All efficacy analyses were based on data obtained prior to rescue therapy. Treatment with saxagliptin 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 to Week 102. The HbA1c change for

saxagliptin 5 mg plus metformin compared with placebo plus metformin was −0.8% at Week 102.

Coadministration of Saxagliptin with Metformin in Treatment Naive Patients

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 saxagliptin 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: saxagliptin 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. Saxagliptin was dosed once daily. During Weeks 1 through 5, in the saxagliptin 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 saxagliptin 5 mg plus metformin provided significant improvements in HbA1c, FPG, and PPG compared with metformin alone (Table 2). Reductions in HbA1c at Week 4 and FPG at Week 2 were seen in the saxagliptin 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 saxagliptin 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 saxagliptin 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 saxagliptin 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 saxagliptin 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 2 Glycaemic Parameters at Week 24 in a Placebo-Controlled Study of Saxagliptin 5 mg in Combination with Metformin as Initial Therapy and Metformin Alone*

Efficacy Parameter	Saxagliptin 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

Patients who were rescued (based on predefined glucose levels) during the initial 24-week study period as well as those who completed all visits during the initial 24-week study period without need for rescue therapy were eligible to enter a controlled long-term study extension. Patients who received saxagliptin in the initial 24-week study period maintained the same dose of saxagliptin in the long-term extension. All efficacy analyses were based on data obtained prior to rescue therapy. Treatment with saxagliptin 5 mg plus metformin was associated with a greater reduction in HbA1c than in the metformin monotherapy group, and the effect relative to control was sustained to Week 76. The HbA1c change for saxagliptin 5 mg plus metformin compared with metformin monotherapy was −0.5% 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 randomised, double-blind, active-controlled study of 52-week duration, to evaluate the efficacy and safety of saxagliptin in combination with metformin compared with sulfonylurea in combination with metformin in patients with inadequate glycemic 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, two-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 saxagliptin or 5 mg of glipizide in addition to their current dose of open-label metformin. Patients in the glipizide plus metformin group were 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 (mean dose 15 mg).

Saxagliptin 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 3). The intent-to-treat analysis showed consistent results.

Saxagliptin 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 saxagliptin exhibited a significant decrease 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 3 HbA1c at Week 52 in an Active-Controlled Study of Saxagliptin in Combination with Metformin*

Efficacy Parameter	**Saxagliptin 5 mg + Metformin**	**Glipizide + Metformin**
HbA1c (%)	**N=293**	**N=293**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean[†])	−0.7	−0.8
Difference vs glipizde+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%

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 saxagliptin as add-on therapy to a basal or pre-mixed insulin in patients with inadequate glycaemic control (HbA1c ≥7.5% and ≤11%) on a basal or pre-mixed insulin alone (N=141) or on a basal or pre-mixed insulin 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 premixed insulin.

Patients who met eligibility criteria were enrolled in a single-blind, four-week, dietary and exercise placebo lead-in period during which patients received insulin (and metformin, if applicable) at their prestudy dose(s). Following the lead-in period, eligible patients were randomised to saxagliptin 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 saxagliptin and metformin (if applicable) were not allowed in this study.

Saxagliptin 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 4). Similar HbA1c reductions versus placebo were achieved for patients using saxagliptin 5 mg add-on to insulin alone and saxagliptin 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 saxagliptin 5 mg add-on to insulin group and 32% in the placebo add-on to insulin group.

Table 4 Glycaemic Parameters at Week 24 in a Placebo-Controlled Study of Saxagliptin 5 mg as Add-on Combination Therapy with Insulin*

Efficacy Parameter	Saxagliptin 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)
2- hour PPG (mmol/L)	**N=262**	**N=129**
Baseline (mean)	13.9	14.1
Change from baseline (adjusted mean†)	−1.5	−0.2
Difference from placebo (adjusted mean†)	−1.3¶	
95% Confidence Interval	(−2.1, −0.5)	
FPG (mmol/L)	**N=300**	**N=149**
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)	
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 or last observation 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 plus 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 saxagliptin and placebo groups, respectively. No therapeutic interaction was seen with metformin in this study.

INDICATIONS

KOMBIGLYZE is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

CONTRAINDICATIONS

KOMBIGLYZE is contraindicated in patients with:

- a history of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to any DPP4 inhibitor. Hypersensitivity to the active substances or to any of the excipients; (See **Precautions**);
- diabetic ketoacidosis, diabetic pre-coma;
- moderate or severe renal impairment (creatinine clearance < 60 ml/min) (See **Precautions**);
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, or intravascular administration of iodinated contrast agents (See **Precautions**);
- acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, pulmonary embolism, recent myocardial infarction, shock, acute significant blood loss, sepsis, gangrene, pancreatitis;
- during or immediately following surgery where insulin is essential, elective major surgery;
- hepatic impairment;
- acute alcohol intoxication, alcoholism;
- lactation.

PRECAUTIONS

General

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

Lactic acidosis

Metformin hydrochloride

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with KOMBIGLYZE; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterised by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilised on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal, but less than 5 mmol/L, in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (see **Contraindications**).

Hypersensitivity Reactions

Saxagliptin

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 KOMBIGLYZE, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See **Contraindications** and **Adverse effects.**)

Pancreatitis

Saxagliptin

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, KOMBIGLYZE should be discontinued. (See **Adverse effects**.)

Renal Function

Metformin hydrochloride

Metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive KOMBIGLYZE. In the elderly, KOMBIGLYZE should be carefully titrated to establish the minimum dose for adequate glycaemic effect because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, KOMBIGLYZE should not be titrated to the maximum dose of the metformin component. (See **Precautions**).

Before initiation of KOMBIGLYZE therapy, and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (eg the elderly, patients being initiated on antihypertensives, diuretics or NSAIDs), renal function should be assessed more frequently and KOMBIGLYZE discontinued if evidence of renal impairment is present. (See **Dosage and Administration**).

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

Metformin hydrochloride

A patient with type 2 diabetes previously well controlled on KOMBIGLYZE who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, KOMBIGLYZE must be stopped immediately and other appropriate corrective measures initiated.

Impaired Hepatic Function

Metformin hydrochloride

Since impaired hepatic function has been associated with some cases of lactic acidosis, KOMBIGLYZE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Administration of Iodinated contrast agent

Metformin hydrochloride

The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving metformin. Therefore, KOMBIGLYZE should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (See **Contraindications**)

Hypoxic States

Metformin hydrochloride

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

Surgery

Metformin hydrochloride

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

Vitamin B12 Levels

Metformin hydrochloride

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on KOMBIGLYZE and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at 2- to 3-year intervals may be useful.

Alcohol Intake

Metformin hydrochloride

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

Loss of Control of Blood Glucose

Metformin hydrochloride

When a patient stabilised on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold KOMBIGLYZE and temporarily administer insulin. KOMBIGLYZE may be reinstituted after the acute episode is resolved.

Skin disorders

Saxagliptin

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 **Adverse effects**). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.

Immunocompromised patients

Saxagliptin

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.

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 with KOMBIGLYZE or saxagliptin.

Saxagliptin or metformin may have a negligible influence on the ability to drive and use machines. It should be taken into account that dizziness has been reported in studies with saxagliptin.

Effects on fertility

No studies have been conducted with the combined components of KOMBIGLYZE to evaluate effects on fertility.

Saxagliptin

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.

Metformin

Fertility of male and female rats was unaffected by metformin when administered at doses as high as 500 mg/kg/day which is approximately three times the maximum recommended human dose based on body surface area comparisons.

Use in pregnancy – Category C

There are no adequate and well-controlled studies of KOMBIGLYZE or its individual components in pregnant women. Because animal reproduction studies are not always predictive of human response, KOMBIGLYZE, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the maximum recommended human doses (MRHD; saxagliptin 5 mg and metformin 2000 mg), respectively, in rats; and 249 and 1.1 times the MRHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of wavy ribs; associated maternal toxicity was limited to weight decrements of 5% to 6% over the course of gestation days 13 through 18, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to reduced/unformed faeces and transient reductions in food consumption; and developmental toxicity in these litters was limited to fetal body weight decrements of 7%, cases of incompletely ossified pubis and a low incidence of delayed ossification of the fetal hyoid.

Saxagliptin

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.

Metformin

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Use in lactation

No studies in lactating animals have been conducted with the combined components of KOMBIGLYZE. In studies performed with the individual components, both saxagliptin and metformin are secreted in the milk of lactating rats. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE is administered to a nursing woman.

Paediatric use

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

Use in elderly

As saxagliptin and metformin are eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, KOMBIGLYZE should be used with caution as age increases.

Saxagliptin

Of the total number of subjects (N=4148) in six double-blind, controlled clinical safety and efficacy studies of saxagliptin, 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.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. (See **Contraindications**, **Precautions**, and **Pharmacokinetics**).

Genotoxicity

Saxagliptin

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.

Metformin hydrochloride

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

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of KOMBIGLYZE.

Saxagliptin

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.

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

INTERACTIONS WITH OTHER MEDICINES

Saxagliptin

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 co-administration 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 co-administered 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 oestrogen/progestogen combined 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, saxagliptin 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 14%; however, the AUC of saxagliptin was unchanged. The plasma Cmax of glibenclamide increased by 16%; however, the AUC of glibenclamide was unchanged. Therefore, saxagliptin 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, saxagliptin 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, saxagliptin 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, saxagliptin 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, saxagliptin 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} of ketoconazole increased by 13%; however, the AUC of ketoconazole was unchanged. Therefore, saxagliptin 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.

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 saxagliptin 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 saxagliptin 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 saxagliptin 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 saxagliptin 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.

Metformin hydrochloride

Cationic drugs

Cationic drugs (eg, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Glibenclamide

In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glibenclamide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glibenclamide AUC and maximum concentration (C_{max}) were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glibenclamide blood levels and pharmacodynamic effects makes the clinical significance of this interaction uncertain.

Frusemide

A single-dose, metformin-frusemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Frusemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of frusemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in frusemide renal clearance. No information is available about the interaction of metformin and frusemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Use with Other Drugs

Certain drugs tend to produce hyperglycaemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

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.

ADVERSE EFFECTS

Clinical Experience – Saxagliptin

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

In a pre-specified pooled analysis of the 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 saxagliptin 5 mg was similar to placebo.

Discontinuation of therapy due to adverse events was higher in patients who received saxagliptin 5 mg as compared to placebo (3.3% as compared to 1.8%).

Adverse Reactions Associated with Saxagliptin and Concomitant Therapy

In the short-term 24-week add-on to glibenclamide study, the overall incidence of hypoglycaemia was higher for saxagliptin 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 saxagliptin 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 hypoglycemia was 18.2% for saxagliptin 5 mg and 12.0% for up-titrated glibenclamide; the incidence of confirmed hypoglycemia was 1.6% for Saxagliptin 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 saxagliptin 5 mg was similar to placebo (4.8% versus 4.3%). Adverse reactions of hypoglycaemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required.

In the add-on to TZD study, the incidence of peripheral oedema was higher for saxagliptin 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 saxagliptin 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 saxagliptin 5 mg alone or in combination was similar to placebo (1.7% versus 2.4%).

Table 5 Adverse Events reported (regardless of investigator assessment of causality) from a pooled analysis of 5 studies in ≥5% of patients treated with Saxagliptin 2.5 mg or 5 mg as monotherapy or as add-on to metformin, SU* or TZD^.

	Number (%) of Patients		
	Saxagliptin 2.5 mg N=882	**Saxagliptin 5 mg N=882**	**Placebo N=799**
Infections and infestations			
Upper respiratory tract infection	62 (7.0)	68 (7.7)	61(7.6)

	Number (%) of Patients		
	Saxagliptin 2.5 mg N=882	**Saxagliptin 5 mg N=882**	**Placebo N=799**
Urinary tract infection	45 (5.1)	60 (6.8)	49 (6.1)
Nasopharyngitis	50 (5.7)	49 (5.6)	54 (6.8)
Gastrointestinal disorders			
Diarrhoea	53 (6.0)	36 (4.1)	49 (6.1)
Nervous system disorders			
Headache	57 (6.5)	57 (6.5)	47 (5.9)

*glibenclamide ^pioglitazone or rosiglitazone

In the combined short-term and long-term extension period, adverse reactions in placebo controlled studies reported in ≥2% of patients treated with saxagliptin 5 mg or 2.5 mg and ≥1% more frequently compared to placebo were: gastroenteritis, sinusitis, vomiting and abdominal pain.

Adverse reactions Associated with initial combination therapy

In a 24-week, active-controlled study of initial therapy of saxagliptin in combination with metformin, the adverse events reported (regardless of investigator assessment of causality) in ≥5% of patients are shown in Table 6.

Table 6 Initial Therapy with Combination Saxagliptin and Metformin: Adverse Events reported (regardless of investigator assessment of causality) in ≥5% of patients treated with Combination Therapy of Saxagliptin 5 mg Plus Metformin as compared to saxagliptin 10 mg alone and metformin alone)

	Number (%) of Patients	
	Saxagliptin 5 mg + Metformin* N=320	**Metformin* N=328**
Infections and infestations		
Nasopharyngitis	22 (6.9)	13 (4.0)
Gastrointestinal disorders		
Diahorrea	22 (6.9)	24 (7.3)
Nervous system disorders		
Headache	24 (7.5)	17 (5.2)

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

In this study, adverse reactions that were reported in ≥2% of patients treated with saxagliptin 5 mg and ≥1% more frequently compared to metformin included the following: upper respiratory tract infection, bronchitis, dyspepsia, arthralgia and back pain.

Hypertension, an adverse event of uncertain causality, was reported in ≥2% of patients treated with saxagliptin 5 mg and ≥1% more frequently compared to placebo

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

Hypoglycaemia

Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidence of reported hypoglycaemia for saxagliptin 5 mg versus placebo given as monotherapy was 5.6% versus 4.1%, respectively, and 5.8% versus 5% given as add-on therapy to metformin.

In the initial combination therapy study the incidence of hypoglycaemia was 3.4% in patients given saxagliptin 5 mg plus metformin and 4.0% in patients given metformin alone. In the combined short-term and long-term extension period, the incidence of hypoglycaemia was 4.7% in patients given saxagliptin 5 mg plus metformin, and 6.1% in patients given metformin alone.

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

Hypersensitivity Reactions

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 saxagliptin 5 mg and placebo, respectively. None of these events in patients who received saxagliptin required hospitalisation or were reported to be life-threatening by the investigators.

Adverse Reactions Associated with Saxagliptin Coadministered with Metformin in Treatment-Naive Patients with Type 2 Diabetes

In the initial combination of saxagliptin 5 mg with metformin therapy, the incidence of nasopharyngitis was common and higher for saxagliptin plus metformin (6.9%) as compared to saxagliptin 10 mg (4.2%) and metformin alone (4.0%). The incidence of headache was common and higher for saxagliptin 5 mg plus metformin (7.5%) as compared to saxagliptin 10 mg (6.3%) and metformin alone (5.2%).

Laboratory Findings - Saxagliptin

Across clinical studies, the incidence of laboratory adverse events was similar in patients treated with saxagliptin 5 mg compared to patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, a mean decrease of approximately 100 cells/microL relative to placebo was observed in a pooled analysis of five placebo-controlled clinical studies. Mean absolute lymphocyte counts remained stable and within normal limits with daily dosing up to 102 weeks in duration. 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 – saxagliptin

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**.)

Metformin hydrochloride

Metformin adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from the metformin Product Information available in Australia.

Gastrointestinal

Very common: Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite) are the most frequent reactions to metformin (> 1/10), especially during the initial treatment period. These symptoms are generally transient and resolve spontaneously during continued treatment.

Occurrence of gastrointestinal symptoms, once a patient is stabilised on any dose of metformin, could be due to lactic acidosis or other serious disease.

Systemic/metabolic

Very rare: Lactic acidosis (see **Precautions**) is a very rare (< 1/10,000) but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin.

The onset of lactic acidosis is often subtle and accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Lactic acidosis should be suspected in any diabetic

patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in hospital. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted.

Nervous System Disorders

Common: Taste disturbance (3%) is common.

Dermatological

Very rare: Skin reactions such as erythema, pruritus and urticaria have been reported, but the incidence is very rare (< 1/10,000).

Haematological

Very rare: A decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long term with metformin (< 1/10,000). Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia. Therefore, serum B12 levels should be appropriately monitored or periodic parenteral B12 supplementation considered.

Hepatobiliary Disorders

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, have been reported.

In clinical trials in children and adolescents with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

DOSAGE AND ADMINISTRATION

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment, other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per day.

KOMBIGLYZE should be taken with or after food.

For patients inadequately controlled on a maximally tolerated dose of metformin monotherapy:

For patients not adequately controlled on metformin alone, the dose of KOMBIGLYZE should provide a total daily dose of saxagliptin 5 mg, dosed as 2.5 mg twice daily, plus the dose of metformin already being taken.

For patients switching from coadministration of saxagliptin and metformin:

For patients switching from coadministration of saxagliptin and metformin, KOMBIGLYZE should be initiated at the dose of saxagliptin and metformin already being taken.

Coadministration with insulin

For patients inadequately controlled on dual combination therapy of insulin and metformin, or for patients controlled on triple combination therapy of insulin and metformin plus saxagliptin as separate tablets, the dose of KOMBIGLYZE should provide saxagliptin 2.5mg twice daily (5mg total daily dose) and the dose of metformin similar to the dose already being taken.

KOMBIGLYZE 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.

For patients as a initial combination therapy

The recommended starting doses of KOMBIGLYZE when used as initial combination therapy is one 2.5 mg/500 mg tablet twice daily. Patients with inadequate glycaemic control on this starting dose should further have their metformin dose increased to 2.5 mg/850 mg twice daily or 2.5 mg/1000 mg twice daily as appropriate.

The following dosage forms are available:

- KOMBIGLYZE (saxagliptin/metformin HCl immediate-release) tablets 2.5 mg/500 mg
- KOMBIGLYZE (saxagliptin/metformin HCl immediate-release) tablets 2.5 mg/850 mg
- KOMBIGLYZE (saxagliptin/metformin HCl immediate-release) tablets 2.5 mg/1000 mg

Renal Impairment

KOMBIGLYZE is contraindicated in patients with renal impairment. (See **Contraindications)**

Hepatic Impairment

Since impaired hepatic function has been associated with some cases of lactic acidosis in patients taking metformin, KOMBIGLYZE should generally be avoided inpatients with clinical or laboratory evidence of hepatic impairment. (See **Precautions** - Hepatic Impairment).

Paediatric and Adolescent

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

Use in Elderly

Saxagliptin and metformin are eliminated in part by the kidney, and therefore, because elderly patients are more likely to have decreased renal function, KOMBIGLYZE should be used with caution as age increases. (See **Precautions** – Use in elderly.)

OVERDOSAGE

Saxagliptin

Once-daily, orally-administered saxagliptin 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 [RHD]).

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 haemodialysis (23% of dose over four hours).

Metformin

High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital. The most effective method to remove lactate and metformin is haemodialysis. Events of hypoglycemia have been reported with overdoses of metformin, although a causal association has not been established.

Contact the Poisons Information Centre on 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

- KOMBIGLYZE (saxagliptin/metformin HCl immediate-release)
  2.5 mg/500 mg tablets are pink, biconvex, round, film-coated tablets with "2.5/500" printed on one side and "4245" printed on the reverse side, in blue ink.

- KOMBIGLYZE (saxagliptin/metformin HCl immediate-release)
  2.5 mg/850 mg tablets are light brown to brown, biconvex, round, film-coated tablets with "2.5/850" printed on one side and "4246" printed on the reverse side, in blue ink.

- KOMBIGLYZE (saxagliptin/metformin HCl immediate-release) 2.5 mg/1000 mg tablets are pale yellow to light yellow, biconvex, oval-shaped, film-coated tablets with “2.5/1000” printed on one side and “4247” printed on the reverse side, in blue ink.

KOMBIGLYZE tablets are available in blister packs of 14 and 56 tablets. The tablets should be stored below 25°C.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF APPROVAL

Date of approval: 1 May 2013