AUSTRALIAN PRODUCT INFORMATION

KOMBIGLYZE® XR (saxagliptin/metformin hydrochloride) modified release tablets

1 NAME OF THE MEDICINE

Saxagliptin (as hydrochloride)/ metformin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KOMBIGLYZE XR is available as:

- KOMBIGLYZE XR 5/500 tablets containing 5 mg saxagliptin (as hydrochloride) immediate release and 500 mg metformin hydrochloride modified release
- KOMBIGLYZE XR 5/1000 tablets containing 5 mg saxagliptin (as hydrochloride) immediate release and 1000 mg metformin hydrochloride modified release
- KOMBIGLYZE XR 2.5/1000 tablets containing 2.5 mg saxagliptin (as hydrochloride) immediate release and 1000 mg metformin hydrochloride modified release

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

3 PHARMACEUTICAL FORM

Modified release tablets.

- KOMBIGLYZE XR 5/500 modified release tablets are light brown to brown, biconvex, capsule shaped, film-coated tablets, with "5/500" printed on one side and "4221" printed on the other side, in blue ink.
- KOMBIGLYZE XR 5/1000 modified tablets are pink, biconvex, capsule shaped, film-coated tablets, with "5/1000" printed on one side and "4223" printed on the other side, in blue ink.
- KOMBIGLYZE XR 2.5 /1000 modified tablets are pale yellow to light yellow, biconvex, capsule shaped, film-coated tablets, with "2.5/1000" printed on one side and "4222" printed on the other side, in blue ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

KOMBIGLYZE XR 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 (*see Sections 5.1 Pharmacodynamic properties - Clinical Trials* and *4.2 Dose and method of administration* for data on combinations studied).

4.2 Dose and method of 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 XR should be taken with or after food.

The dosage of antihyperglycaemic therapy with KOMBIGLYZE XR should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of saxagliptin 5 mg and metformin extended-release 2000 mg. KOMBIGLYZE XR should generally be administered once daily with the evening meal, with gradual dose titration to reduce the gastrointestinal side effects associated with metformin.

Patients should be informed that KOMBIGLYZE XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of KOMBIGLYZE XR will be eliminated in the faeces as a soft, hydrated mass that may resemble the original tablet.

As add on combination therapy:

If therapy with a combination tablet containing saxagliptin and metformin is considered appropriate, the recommended dose of saxagliptin is 5 mg once daily. The recommended starting dose of metformin extended-release is 500 mg once daily, which can be titrated to 2000 mg once daily. The maximum dose of KOMBIGLYZE XR is saxagliptin 5 mg/metformin extended-release 2000 mg taken as two 2.5 mg/1000 mg tablets once daily.

No studies have been performed specifically examining the safety and efficacy of KOMBIGLYZE XR in patients previously treated with other antihyperglycaemic agents and switched to KOMBIGLYZE XR. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycaemic control can occur.

As initial combination therapy

The recommended starting doses of KOMBIGLYZE XR when used as initial combination therapy is one 5 mg/500 mg tablet once daily. Patients with inadequate glycaemic control on this starting dose should further have their metformin dose increased to 5 mg/1000 mg once daily or two 2.5 mg/1000 mg tablets once daily as appropriate.

Special patient populations

Renal impairment

Assess renal function prior to initiation of KOMBIGLYZE XR and periodically thereafter (*see Sections 4.4 Special warnings and precautions for use – Use in Renal Impairment and 5.2 Pharmacokinetic properties – Special Populations (Renal impairment)*). Factors that may increase the risk of lactic acidosis (*see Section 4.4 Special warnings and precautions for use*) should be reviewed before considering initiation of KOMBIGLYZE XR in patients with eGFR < 60 mL/min/1.73m^2.

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

No dosage adjustment is required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2 (by Modified Diet in Renal Disease [MDRD] eGFR equation).

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

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

It is not recommended to initiate treatment with KOMBIGLYZE XR in patients with eGFR <45 mL/min/1.73 m^2. If during treatment eGFR falls to levels persistently below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy and limit the maximum dose of KOMBIGLYZE XR to 2.5 mg/1000 mg once daily (*see 4.4 Special warnings and precautions for use - Use in Renal Impairment*).

Severe Renal Impairment (eGFR < 30 mL/min/1.73 m^2)

KOMBIGLYZE XR is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). (*See section 4.3 Contraindications*)

Table 1 Dosage in patients with renal impairment

eGFR mL/min/ 1.73 m^2 *	Metformin	Saxagliptin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum total daily dose is 5 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum total daily dose is 5 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum total daily dose is 2.5 mg.
<30	Metformin is contraindicated.	Maximum total daily dose is 2.5 mg.

*GFR was originally used to establish these dosing categories based on renal function, all values were normalized to an average surface area (size) of 1.73m2. As eGFR is considered a reasonable estimate of GFR and is more widely used in clinical practice, treatment recommendations in this prescribing information are based on eGFR.

Hepatic impairment

Since impaired hepatic function has been associated with some cases of lactic acidosis in patients taking metformin, KOMBIGLYZE XR should be avoided inpatients with clinical or laboratory evidence of hepatic impairment. (See *section 4.4 Special warnings and precautions for use – Use in Hepatic Impairment*).

Paediatric and Adolescent

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

Use in the 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 XR should be used with caution as age increases. (See *Section 4.4 Special warnings and Precautions for use – Use in the elderly*.)

4.3 Contraindications

KOMBIGLYZE XR is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients, or a history of any serious hypersensitivity reaction, including anaphylactic reaction and angioedema, to any dipeptidyl peptidase 4 (DPP4) inhibitor (*see Sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects*);
- Metabolic acidosis: Acute or chronic metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- Diabetic pre-coma;
- Severe renal impairment (eGFR < 30 mL/min/1.73 m2) (*see Section 4.4 Special warnings and precautions for use – Use in Renal Impairment*);

- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, or intravascular administration of iodinated contrast agents (*see Section 4.4 Special warnings and precautions for use*);
- 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.

4.4 Special warnings and precautions for use

General

KOMBIGLYZE XR should not be used in patients with type 1 diabetes mellitus. KOMBIGLYZE XR has not been studied in combination with GLP-1 agonists (e.g. exenatide, liraglutide).

Lactic acidosis

Metformin hydrochloride

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

Medicinal products that can acutely impair renal function, such as antihypertensives, diuretics and NSAIDs, should be initiated with caution in metformin-treated patients (*see also Section 4.5 Interaction with other medicines and other forms of interactions*).

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterized by symptoms such as acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. Lactic acidosis is a medical emergency that must be treated in a hospital setting. If metabolic acidosis is suspected, treatment with KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately.

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 XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. (*See sections 4.3 Contraindications* and *4.8 Adverse effects (Undesirable effects)*.)

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 XR should be discontinued. (See *4.8 Adverse effects (Undesirable effects)- Postmarketing experiene*.)

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

Use in Renal Impairment

Metformin hydrochloride

As metformin is excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function, assess renal function prior to initiation of KOMBIGLYZE XR and then periodically thereafter:

- at least annually
- at least two to four times per year in patients with renal function where eGFR levels are approaching 45 mL/min/1.73 m^2 and in elderly patients.

It is not recommended to initiate treatment with KOMBIGLYZE XR in patients with eGFR < 45 mL/min/1.73 m^2.

If during treatment eGFR falls to levels persistently below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy and limit the maximum dose of KOMBIGLYZE XR to 2.5 mg/1000 mg once daily (*see Section 4.2 Dosage and method of administration – Special patient populations (Renal Impairment)*).

KOMBIGLYZE XR is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see *Section 4.3 Contraindications*).

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 XR 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 XR must be stopped immediately and other appropriate corrective measures initiated.

Use in Hepatic Impairment

Metformin hydrochloride

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

Radiologic studies with intravascular iodinated contrast materials

Metformin hydrochloride

Intravascular administration of iodinated contrast agents in radiological studies can lead to an acute decrease in renal function and has been associated with lactic acidosis in patients receiving metformin. KOMBIGLYZE XR should temporarily be discontinued prior to, or at the time of the procedure and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be stable (*see Section 4.3 Contraindications*).

Acute conditions associated with hypoxia or impacting renal function

Metformin hydrochloride

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction, and other conditions characterised by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotaemia. Acute conditions such as dehydration, severe infections, and hypoperfusion, have potential to alter renal function. When such events occur in patients on KOMBIGLYZE XR therapy, the drug should be promptly discontinued.

Surgical Procedures

Metformin hydrochloride

Use of KOMBIGLYZE XR should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as stable.

Vitamin B12 Levels

Metformin hydrochloride

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.

Excessive Alcohol Intake

Metformin hydrochloride

Alcohol potentiates the effect of metformin on lactate metabolism. Patients, should be warned against excessive alcohol intake, while receiving KOMBIGLYZE XR.

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 XR and temporarily administer insulin. KOMBIGLYZE XR may be reinstituted after the acute episode is resolved.

Use with medicines 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 KOMBIGLYZE XR. (*See Section 4.8 Adverse effects (Undesirable effects)*.)

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

Bullous pemphigoid

Post-marketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving KOMBIGLYZE XR. If bullous pemphigoid is suspected, KOMBIGLYZE XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (*see Section 4.8 Adverse effects (undesirable effects – Postmarketing experience).*

Cardiac failure

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

Arthralgia

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

Immunocompromised patients

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.

Use in the 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 XR should be used with caution as age increases.

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

Of the total number of subjects (N=4148) 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, 75 years and over and younger subjects.

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 the risk of serious adverse reactions to the drug is greater in patients with impaired 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 Sections *4.3 Contraindications*, *4.4 Special warnings and precautions for use*, and *5.2 Pharmacokinetic properties*).

Paediatric use

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

Effects on laboratory tests

No data available

4.5 Interactions with other medicines and other forms of interactions

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 coadministration with inhibitors or inducers of CYP3A4/5.

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

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

In studies conducted in healthy subjects, the pharmacokinetics of saxagliptin, and its major metabolite, were altered by some drugs which affect the CYP3A4/5 system. However, total exposure of the total active components of saxagliptin (parent + metabolite), was not meaningfully

altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole, rifampicin, omeprazole, aluminium hydroxide + magnesium hydroxide + simethicone combination, or famotidine. Saxagliptin also did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole or an oestrogen/progestogen 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 glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. 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 hypoglycaemia.

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 KOMBIGLYZE XR have not been specifically studied.

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

No studies have been conducted with the combined components of KOMBIGLYZE XR 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 XR or its individual components in pregnant women. Because animal reproduction studies are not always predictive of human response, KOMBIGLYZE XR, 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 hydrochloride

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 XR. 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 XR is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with KOMBIGLYZE XR 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.

4.8 Adverse effects (Undesirable effects)

Significant adverse events are also described in the Precautions section.

Clinical Experience – Saxagliptin

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

Adverse Reactions Associated with Saxagliptin in the SAVOR Trial

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

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

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

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

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

Hypoglycaemia

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

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

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

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

Saxagliptin in Studies of Glycaemic control

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. In the 24-week short-term period, discontinuation of therapy due to adverse events occurred in 3.3% and 1.8% of patients receiving saxagliptin 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 saxagliptin 5 mg and placebo, respectively.

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

Table 2 Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies* Reported in ≥5% of Patients Treated with saxagliptin 5 mg and More Commonly than in Patients Treated with Placebo

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

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

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

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

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

Adverse Reactions Associated with Saxagliptin and Concomitant Therapy

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 and ≥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 ≥2% of patients treated with saxagliptin 5 mg and ≥1% more frequently compared to placebo.

In a 24-week, active-controlled study of initial therapy of saxagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients are shown in Table 3.

Table 3 Initial Therapy with Combination of Saxagliptin and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of Saxagliptin 5 mg Plus Metformin (and Greater Than in Patients Treated with Saxagliptin 10 mg Alone and Metformin Alone)

	Number (%) of patients		
	Saxagliptin 5 mg + Metformin*	Saxagliptin 10 mg	Metformin*
	N=320	N=335	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 of initial therapy of saxagliptin in combination with metformin, less common adverse events that were reported in ≥2% of patients treated with saxagliptin 5 mg and ≥1% more frequently compared to saxagliptin monotherapy and metformin included the following: bronchitis, dyspepsia, and back pain.

Peripheral Oedema

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

Hypoglycaemia

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

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

In the 24-week study of initial therapy of saxagliptin in combination with metformin 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 4.4% in patients given saxagliptin 5 mg plus metformin, and 5.2% in patients given metformin alone.

In the short-term 24-week add-on to glibenclamide study, the overall incidence of hypoglycaemia was higher for 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 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 hypoglycaemia was 18.2% for saxagliptin 5 mg and 12.0% for up-titrated glibenclamide; the incidence of confirmed hypoglycaemia was 1.6% for saxagliptin 5 mg and 1.9% for up-titrated glibenclamide.

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

In the analysis of pooled safety data of 1169 patients from trials evaluating saxagliptin in combination with dapagliflozin, the overall incidence of hypoglycaemia for the pooled safety data of was low (≤1.8% in any treatment group); there was no increase in hypoglycaemia in saxagliptin plus dapagliflozin plus metformin treatment group compared to the saxagliptin plus metformin or

dapagliflozin plus metformin treatment groups. The combined use of saxagliptin plus dapagliflozin plus metformin was not associated with an increase in the risk of hypoglycaemia when compared to the individual agents as monotherapy. This was consistent with prior clinical trial experience regardless of whether the combination was added to metformin concurrently or sequentially.

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

Vital signs

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

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

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

Postmarketing experience – saxagliptin

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

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 *Section 4.4 Special warnings and precautions for use – Lactic acidosis*) 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.

Reporting of suspected adverse reactions

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

4.9 Overdose

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 hydrochloride

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 hypoglycaemia have been reported with overdoses of metformin, although a causal association has not been established.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

KOMBIGLYZE XR 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 DPP-4 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 hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, *see Section 4.4 Special warnings and precautions for use*) and does not cause hyperinsulinaemia. 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.

Pharmacodynamics

Improvement in glycaemic control

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

Improved Glycaemic Control

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 XR; however, bioequivalence of KOMBIGLYZE XR with coadministered saxagliptin and metformin hydrochloride extended release tablets was demonstrated.

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 glycaemic 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 (Table 4). 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

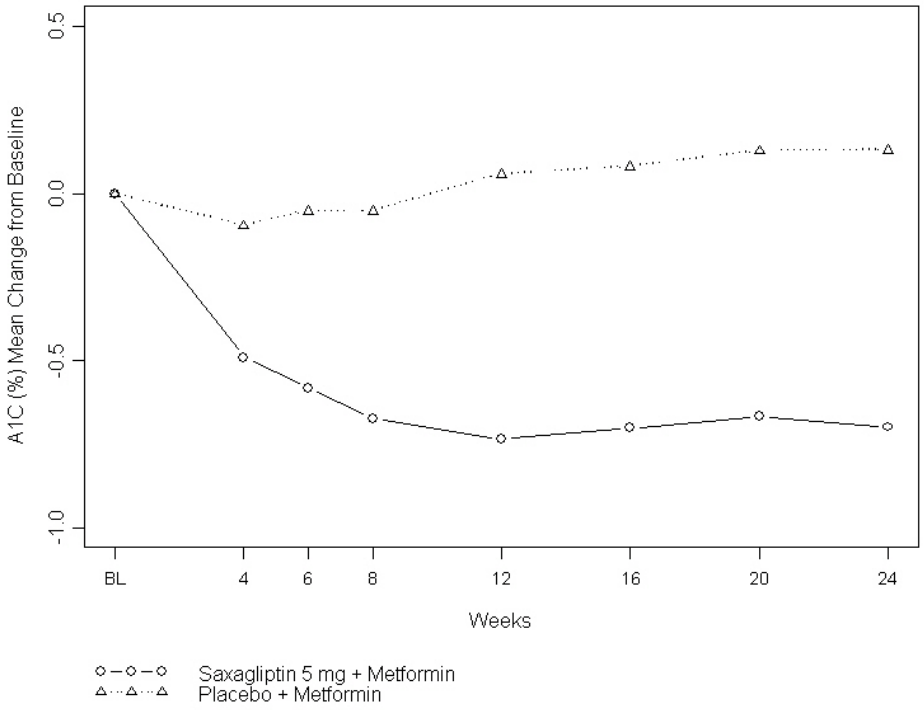
patients who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria was higher in the placebo plus metformin group (27%) than in the saxagliptin 5 mg plus metformin group (13%). Higher baseline HbA1c was associated with a greater adjusted mean change 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 4 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
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 5). 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 5 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.

Saxagliptin 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 glycaemic control (HbA1c >6.5% and ≤10%) on metformin alone. Patients were required to be on a stable dose of metformin (at least 1500 mg daily) for at least 8 weeks to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 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 6). 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 6 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)	7.5	7.5
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%

Controlled Long-Term Study Extension

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

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

Saxagliptin 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 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 7). 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 7 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

Efficacy Parameter	Saxagliptin 5 mg + Insulin (+/− Metformin) N=304	Placebo + Insulin (+/− Metformin) N=151
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.

Controlled Long-Term Study Extension

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

Saxagliptin in Combination with Metformin plus a Sulfonylurea

A total of 257 patients with type 2 diabetes participated in this randomised, double-blind, placebo-controlled trial of 24-week duration to evaluate the efficacy and safety of saxagliptin in combination

with metformin plus a sulfonylurea in patients with inadequate glycaemic control (HbA1c ≥7% and ≤10%). Patients were to be on a stable combined dose of metformin extended-release or immediate-release (at maximum tolerated dose with minimum dose for enrolment being 1500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrolment being ≥50% of the maximum recommended dose) for at least eight weeks prior to enrolment.

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

In combination with metformin and a sulfonylurea, saxagliptin provided significant improvements in HbA1c and PPG compared with placebo plus metformin and sulfonylurea (Table 8)

Table 8 Glycaemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Metformin plus Sulfonylurea*

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

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

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

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

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone (HbA1c≥8% and ≤12%) participated in this 24-week randomised, double blind, active comparator-controlled superiority trial with the combination of saxagliptin and dapagliflozin added concurrently to metformin, versus saxagliptin (DPP4 inhibitor) or dapagliflozin (SGLT2 inhibitor) added to metformin. Patients were randomised to one of three double-blind treatment groups to receive saxagliptin 5 mg and dapagliflozin 10 mg added to metformin XR, saxagliptin 5 mg and placebo added to metformin XR, or dapagliflozin 10 mg and placebo added to metformin XR. The saxagliptin and dapagliflozin combination group achieved significantly greater reductions in HbA1c versus either saxagliptin group or dapagliflozin group at 24 weeks (see Table 9).

Table 9 HbA1c at Week 24 (LRM[a]) in Active-Controlled Study Comparing the Combination of Saxagliptin and Dapagliflozin Added Concurrently to Metformin with either Saxagliptin or Dapagliflozin Added to Metformin

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

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

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

[c] Least squares mean adjusted for baseline value.

[d] p-value < 0.0001.

[e] p-value=0.0166

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

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

Table 10 HbA1c change from baseline at Week 24 (excluding data after rescue) for randomised subjects in studies assessing sequential addition of saxagliptin to a background of dapagliflozin and metformin

Efficacy Parameter	Saxagliptin 5 mg + Metformin plus Sulfonylurea N=129	Placebo + Metformin plus Sulfonylurea N=128
HbA1c (%)at week 24[a]		
Baseline (mean)	7.95	7.85
Change from baseline (adjusted mean[b]) (95% CI)	−0.51 (−0.63, −0.39)	−0.16 (−0.28, −0.04)
Comparison of saxa added to dapa+met vs.placebo+saxa+met - adjusted mean[b] (95% CI)	−0.35 (−0.52, −0.18) p-value <0.0001	
Subjects (%) achieving HbA1c < 7% Adjusted for baseline	35.3	23.1

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

[a] Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[b] Least squares mean adjusted for baseline value.

saxa= saxagliptin; dapa=dapagliflozin; met=metformin

Cardiovascular safety

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the effect of saxagliptin on the occurrence of major cardiovascular disease (CVD) events was assessed in 16,492 adult patients with type 2 diabetes who had either established CVD or multiple risk factors for vascular disease. Patients were randomly assigned to placebo (n=8212) or saxagliptin (5 mg or 2.5 mg for patients with moderate or severe renal insufficiency) once daily (n=8280). The demographics and baseline characteristics of subjects were balanced between the saxagliptin and placebo groups (see Table 11). Subjects were followed for a mean duration of 2 (median=2.0) years.

Table 11 Demographic and Diabetes-Related Baseline Characteristics (SAVOR ITT population

Parameter		Saxagliptin (N=8280)	Placebo (N=8212)
Gender, n (%)	Male	5512 (66.6)	5525 (67.3)
	Female	2768 (33.4)	2687 (32.7)
Age (years)[a]	Mean (min, max)	65.1 (39.0, 99.0)	65.0 (40.0, 93.0)
Age group (years)[a], n (%)	≥65	4290 (51.8)	4271 (52.0)
	≥75	1169 (14.1)	1161 (14.1)
Duration of T2DM (years)	Mean (min, max)	12.0 (0.0, 60.9)	11.9 (0.0, 60.7)
HbA1C (%), n (%)	≥7	6097 (73.6)	5983 (72.9)
eGFR category (mL/min)[b], n (%)	>50	6986 (84.4)	6930 (84.4)
	≥30 to ≤ 50	1122 (13.6)	1118 (13.6)
	<30	172 (2.1)	164 (2.0)

Parameter		Saxagliptin (N=8280)	Placebo (N=8212)
CV risk			
Subjects with MRF[c], n (%)		1789(21.6)	1747 (21.3)
Subjects with established CVD[d], n (%)		6494 (78.4)	6465 (78.7)
Baseline diabetes medication, n (%)	Metformin	5765 (69.6)	5658 (68.9)
	Insulin	3423 (41.3)	3364 (41.0)
	Sulfonylurea	3327 (40.2)	3259 (39.7)
	Thiazolidinedione	510 (6.2)	460 (5.6)
Baseline CVD medication, n (%)	ACE inhibitor/ARB	6478 (78.2)	6517 (79.4)
	Statin	6482 (78.3)	6435 (78.4)
	Aspirin	6249 (75.5)	6155 (75.0)
	Beta-blockers	5101 (61.6)	5061 (61.6)
	Non-aspirin anti-platelet medication	1986 (24.0)	1960 (23.9)

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

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

The primary safety and efficacy endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following major adverse CV events (MACE): CV death, nonfatal myocardial infarction, or nonfatal ischaemic stroke. The primary and secondary end-points are described in Table 12.

Table 12 Primary and secondary SAVOR study objectives

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

Saxagliptin did not increase the CV risk (CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke) in patients with T2DM compared to placebo when added to current background therapy (HR 1.00; 95% CI: 0.89, 1.12; P<0.001 for non-inferiority). No increased risk for the primary endpoint was observed between saxagliptin and placebo in any of the following subgroups:

CVD, multiple risk factors for CVD, mild, moderate, or severe renal impairment, age, gender, race, region, duration of type 2 diabetes, history of heart failure, baseline HbA1c, albumin/creatinine ratio, baseline antidiabetic medication, or baseline use of statins, aspirin, ACE inhibitors, ARBs, beta-blockers, or antiplatelet medications.

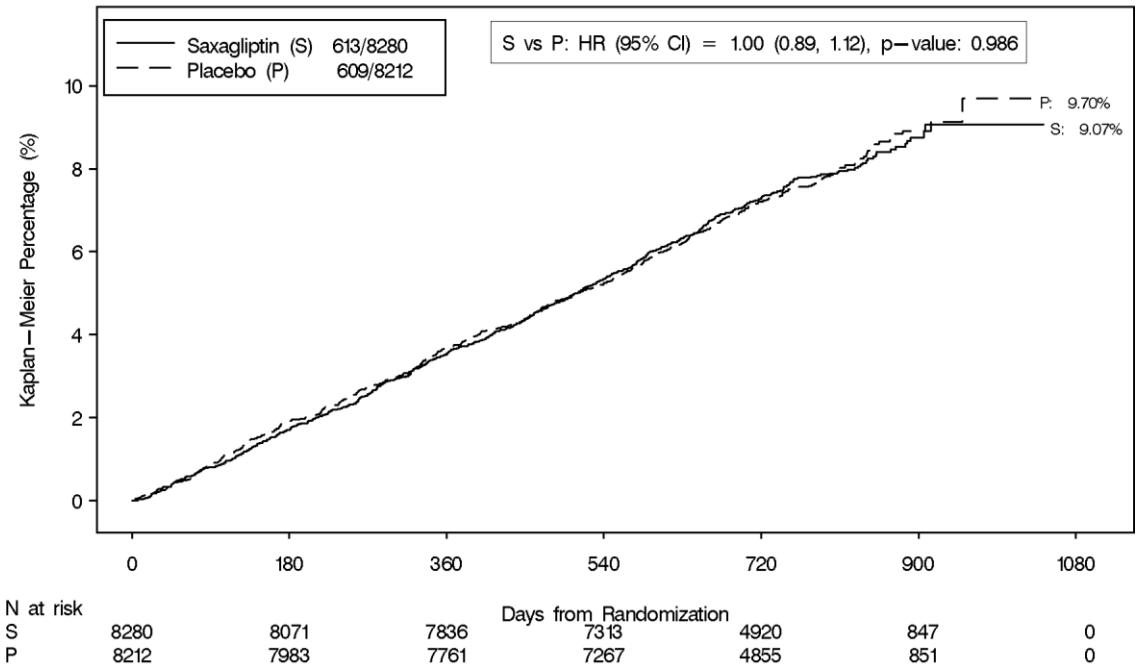
The primary efficacy endpoint did not demonstrate a statistically significant difference in major adverse coronary events for saxagliptin compared to placebo when added to current background therapy in patients with T2DM.

Table 13 Primary and Secondary Clinical Endpoints by Treatment Group in the SAVOR study*

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

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

Figure 2 Cumulative percent of time to first CV event for primary composite endpoint*



* Intent-to-treat population

One component of the secondary composite endpoint, hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance (ie, without adjustment for testing of multiple endpoints) favouring placebo [HR = 1.27; (95% CI: 1.07, 1.51); P = 0.007]. Clinically relevant factors predictive of increased relative risk with saxagliptin treatment could not be definitively identified. Subjects at higher risk for hospitalisation for heart failure, irrespective of treatment assignment, could be identified by known risk factors for heart failure such as baseline history of heart failure or impaired renal function. However, subjects on saxagliptin with a history of heart failure or impaired renal function at baseline were not at an increased risk relative to placebo for the primary or secondary composite endpoints or all-cause mortality.
Additional endpoints in the SAVOR trial included assessment of the parameters used measure glycaemic control and whether treatment with saxagliptin compared with placebo would result in a reduction in the need for increase in dose or addition of new antidiabetic medication. Despite active management of concomitant antidiabetic therapy in both study arms, mean HbA1c levels were lower in the saxagliptin group compared to the placebo group at Year 1 (7.6% versus 7.9%, difference of -0.35% [95% CI: -0.38, -0.31]) and at Year 2 (7.6% versus 7.9%, difference of -0.30% [95% CI: -0.34, -0.26]). The proportions of subjects with HbA1c <7% in the saxagliptin group compared to the placebo group were 38% versus 27% at Year 1 and 38% versus 29% at Year 2. Compared to placebo, saxagliptin resulted in less need for the initiation of new or increases in current oral diabetes medications or insulin. The improvements in HbA1c and the proportion of subjects reaching HbA1c targets among saxagliptin-treated subjects were observed despite lower rates of upward adjustments in diabetes medications or initiation of new diabetes medications or insulin compared with placebo.

5.2 Pharmacokinetic properties

The results of bioequivalence studies in healthy subjects demonstrated that KOMBIGLYZE XR combination tablets are bioequivalent to coadministration of corresponding doses of saxagliptin and metformin hydrochloride modified-release as individual tablets.

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

Saxagliptin

The pharmacokinetics of saxagliptin have 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.

Metformin hydrochloride

Metformin extended-release C_{max} is achieved with a median value of 7 hours. The extent of metformin absorption from the metformin extended-release tablet is increased by approximately 50% when given with food. At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg. After repeated administration of metformin extended-release, metformin did not accumulate in plasma. Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism.

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

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 µg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. Although the extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin extended-release.

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

Distribution studies with extended-release metformin have not been conducted; however, 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 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

Saxagliptin

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 renal impairment with > CrCL50 mL/min (approximately corresponding to eGFR ≥ 45 mL/min/1.73 m^2), the AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than AUC values in subjects with normal renal function. Increases of this magnitude are not clinically relevant, therefore dosage adjustment in these patients is not recommended.

In subjects with renal impairment with CrCL≤50 mL/min (approximately corresponding to eGFR <45 mL/min/1.73 m^2), the AUC values of saxagliptin and its major metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. In these patients, the dose is 2.5 mg once daily (see *Sections 4.2 Dosage and method of administration – Special patient populations (Renal impairment) and 4.4 Special warnings and precautions for use – Use in renal impairment*)

Saxagliptin is removed by hemodialysis.

Metformin hydrochloride

In patients with renal impairment, the plasma and blood half-life of metformin is prolonged in proportion to the decrease in renal function.

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 antihyperglycaemic 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.

5.3 Preclinical safety data

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 XR.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film-coated tablet of KOMBIGLYZE XR contains the following inactive ingredients: carmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, macrogol 3350, titanium dioxide, purified talc, iron oxide red CI77491 (5 mg/500 mg and 5 mg/1000 mg tablets), iron oxide yellow CI77492 (5 mg/500 mg and 2.5 mg/1000 mg tablets) and Opacode monogramming ink S-1-10619 Blue.

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special precautions for storage

The tablets should be stored below 30°C.

6.5 Nature and contents of container

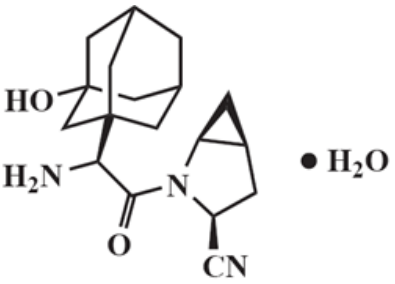
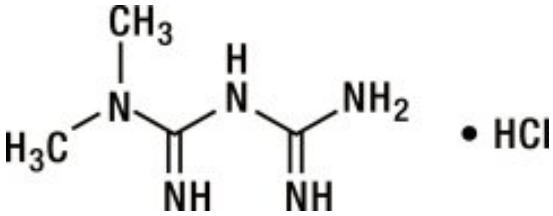
- KOMBIGLYZE XR 5/500 are available in aluminium/ aluminium blister packs of 7 and 28 tablets.
- KOMBIGLYZE XR 5/1000 are available in aluminium/ aluminium blister packs of 7 and 28 tablets.
- KOMBIGLYZE XR 2.5/1000 are available in aluminium/ aluminium blister packs of 14 and 56 tablets.

6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure

	Saxagliptin	**Metformin hydrochloride**
		
Chemical name	(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	*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride
Molecular formula	$C_{18}H_{25}N_3O_2 \cdot H_2O$	$C_4H_{11}N_5 \cdot HCl$
Molecular weight	333.43 (monohydrate)	165.63
Physicochemical characteristics	Saxagliptin is a white to light yellow or light brown powder, non hygroscopic, crystalline. 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 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.

CAS number

Saxagliptin	**Metformin hydrochloride**
945667-22-1	1115-70-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

10 October 2013

10 DATE OF REVISION

01 February 2019

Summary table of changes

Section changed	Summary of new information
Various	New PI form
4.2	Renal Updates
4.3	Renal Updates Update of the hypersensitivity Contraindication Update of the lactic acidosis Contraindication
4.4	Renal Updates Various metformin updates to simplify content
5.2	Renal Updates

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