PRODUCT MONOGRAPH

Pr KOMBOGLYZE®

saxagliptin and metformin hydrochloride tablets

(as saxagliptin hydrochloride and metformin hydrochloride)

2.5mg/500mg, 2.5mg/850mg, 2.5mg/1000mg

Oral Antihyperglycemic Agent

DPP-4 inhibitor

Incretin Enhancer

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TABLE OF CONTENTS

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PART I: HEALTH PROFESSIONAL INFORMATION

Note: for additional information on saxagliptin and metformin hydrochloride, consult the individual Product Monographs.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet / 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg	*For a complete listing see Dosage Forms, Composition and Packaging section*.

INDICATIONS AND CLINICAL USE

KOMBOGLYZE (saxagliptin/metformin hydrochloride) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with saxagliptin and metformin or who are inadequately controlled on metformin alone (see CLINICAL TRIALS).

KOMBOGLYZE is indicated for use in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with saxagliptin, metformin and a sulfonylurea or who are inadequately controlled on metformin and a sulfonylurea alone (see CLINICAL TRIALS).

KOMBOGLYZE is indicated for use in combination with premixed or long/intermediate acting insulin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with saxagliptin, metformin and premixed or long/intermediate acting insulin or who are inadequately controlled on metformin and premixed or long/intermediate acting insulin alone (see CLINICAL TRIALS).

Geriatrics (≥ 65 years of age): Saxagliptin and metformin are eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, KOMBOGLYZE should be used with caution as age increases (see WARNINGS AND

PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (< 18 years of age): Safety and effectiveness of KOMBOGLYZE in pediatric patients have not been established. Therefore, KOMBOGLYZE should not be used in this patient population.

CONTRAINDICATIONS

- Unstable and/or insulin-dependent (Type I) diabetes mellitus.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma. Diabetic ketoacidosis should be treated with insulin.
- In patients with a history of lactic acidosis, irrespective of precipitating factors.
- In the presence of renal disease or impairment, and in patients with serum creatinine levels above the upper limit of normal range or abnormal creatinine clearance (<60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia or when renal function is not known.
- In excessive alcohol intake, acute or chronic.
- In patients with moderate and severe hepatic impairment (see WARNINGS and PRECAUTIONS, Hepatic).
- In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- In patients suffering from severe dehydration.
- In patients who have had a history of any hypersensitivity reaction, including anaphylaxis or angioedema, to saxagliptin or to another DPP-4 inhibitor, metformin or to any ingredient in the formulation (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- During pregnancy and breastfeeding (see WARNINGS AND PRECAUTIONS, Special Populations).

KOMBOGLYZE (saxagliptin/metformin hydrochloride) should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see WARNINGS AND PRECAUTIONS, Renal).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with KOMBOGLYZE (saxagliptin/metformin hydrochloride) (see Endocrine and Metabolism, Lactic Acidosis section below).
- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking KOMBOGLYZE, since alcohol intake potentiates the effect of metformin on lactate metabolism (see Endocrine and Metabolism, Lactic Acidosis section below).

Pancreatitis

There have been post-marketing reports of acute and chronic pancreatitis in patients taking saxagliptin. Reports of fatal and non-fatal hemorrhagic or necrotizing pancreatitis were noted in patients taking other members of this class. After initiation of KOMBOGLYZE, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, KOMBOGLYZE should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using KOMBOGLYZE. Risk factors for pancreatitis include a history of pancreatitis, gallstones, alcoholism, or hypertriglyceridemia.

Hypersensitivity Reactions

There have been post-marketing reports of serious hypersensitivity reactions, including anaphylaxis and angioedema, in patients treated with saxagliptin and other members of this class. Exfoliative skin conditions including Stevens-Johnson syndrome have also been reported in patients treated with saxagliptin and other members of this class, although causality with saxagliptin has not been established. Onset of these reactions occurred within the first 3 months after initiation of the treatment, with some reports occurring after the first dose. If a hypersensitivity reaction to KOMBOGLYZE is suspected, discontinue KOMBOGLYZE, assess for other potential causes for the event, and institute alternative treatment for diabetes (see CONTRAINDICATIONS and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Cardiovascular

Saxagliptin

Patients with Congestive Heart Failure: In a post-market placebo-controlled cardiovascular outcomes trial (SAVOR), hospitalization for heart failure occurred at a greater rate in the saxagliptin group (3.5%) compared to the placebo group (2.8%) [HR =1.27; 95% confidence interval 1.07, 1.51]. In the SAVOR trial, 2105 (12.8%) patients had a history of congestive heart failure, of whom 1056 were randomized to saxagliptin treatment. Caution is warranted if KOMBOGLYZE is used in patients with history of congestive heart failure (especially in those patients who also have renal impairment and/or history of myocardial infarction [MI]).

During therapy with KOMBOGLYZE, patients should be observed for signs and symptoms of heart failure. Patients should be advised of characteristics symptoms of heart failure, and to immediately report such symptoms. If heart failure develops, discontinue KOMBOGLYZE and manage according to current standards of care (see ADVERSE REACTIONS, Post-Marketing, Cardiovascular Safety).

Metformin hydrochloride

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

Endocrine and Metabolism

Metformin hydrochloride

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

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.

In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may

significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see CONTRAINDICATIONS).

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

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

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

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

Physicians should instruct their patients to recognize the symptoms which could be a signal of the onset of lactic acidosis. If acidosis of any kind develops, KOMBOGLYZE should be discontinued immediately.

Change in clinical status of previously controlled Type 2 diabetes patients: A type 2 diabetic patient previously well controlled on KOMBOGLYZE 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, KOMBOGLYZE must be stopped

immediately and appropriate corrective measures initiated. (See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis.)

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

Vitamin B_{12} levels:

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on KOMBOGLYZE and any apparent abnormalities should be appropriately investigated and managed (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

Hypoglycemia:

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur in elderly, debilitated, or malnourished patients, those with adrenal or pituitary insufficiency or when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with alcohol.

A lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia when used in combination with KOMBOGLYZE (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions.

Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

The patients should be warned about driving a vehicle or operating machinery under these conditions where risk of hypoglycemia is present.

Musculoskeletal and connective tissue disorders

Severe and Disabling Arthralgia: Severe and disabling arthralgias have been reported post-marketing in patients taking saxagliptin or other DPP-4 inhibitors. Onset of symptoms following initiation of drug therapy varied from one day to years. Saxagliptin is considered a possible cause for severe joint pain. Patients experienced relief of symptoms upon discontinuation of the medication and some experienced recurrence of symptoms with reintroduction of saxagliptin or another DPP-4 inhibitor. If a patient treated with

KOMBOGLYZE, presents with severe joint pain, discontinuation of KOMBOGLYZE and replacement with other antidiabetic medications should be considered (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Hepatic

Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, KOMBOGLYZE is not recommended in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS).

Peri-Operative Consideration

KOMBOGLYZE therapy 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 normal.

Alcohol Intake

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

Renal

See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis, Geriatrics (≥ 65 years of age) and Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION.

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, KOMBOGLYZE should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Use with Potent CYP 3A4 Inducers

Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampin may reduce the glycemic lowering effect of saxagliptin (see DRUG INTERACTIONS).

Immune

Immunocompromised patients: A dose-related mean decrease in absolute lymphocyte count was observed with saxagliptin. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of saxagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g. human immunodeficiency virus) is unknown (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

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.

Skin

Ulcerative and necrotic skin lesions have been reported in monkeys in non-clinical toxicology studies (see Part II: TOXICOLOGY, Chronic Toxicity). Although skin lesions were not observed at an increased incidence in clinical trials, there is limited experience in patients with diabetic skin complications.

Rash is noted as an adverse event for saxagliptin (see ADVERSE REACTIONS, Clinical trial adverse drug reactions). In keeping with routine care of the diabetic patient, monitoring for skin disorders is recommended.

Bullous pemphigoid: Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of saxagliptin and other DPP-4 inhibitors. 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 KOMBOGLYZE. If bullous pemphigoid is suspected, KOMBOGLYZE should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women with KOMBOGLYZE or its individual components (saxagliptin, metformin hydrochloride). As animal reproductive studies are not always predictive of human response, KOMBOGLYZE, like other antidiabetic medications, is not recommended for use in pregnancy (see CONTRAINDICATIONS AND TOXICOLOGY).

Saxagliptin

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

Metformin hydrochloride

Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, insulin should be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Women: No studies in lactating animals have been conducted with the combined components of KOMBOGLYZE. 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 and/or metformin are excreted in human milk. Therefore, KOMBOGLYZE should not be used by a woman who is nursing.

Pediatrics (< 18 years of age): Safety and effectiveness of KOMBOGLYZE in pediatric patients have not been established. Therefore, KOMBOGLYZE should not be used in this patient population.

Geriatrics (≥ 65 years of age):

Saxagliptin and Metformin hydrochloride

Since saxagliptin and metformin are eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, KOMBOGLYZE should be used with caution as age increases (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

In the elderly, KOMBOGLYZE should be carefully titrated to establish the minimum dose for adequate glycemic effect. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, KOMBOGLYZE should not be titrated to the maximum dose of the metformin component (see WARNINGS AND PRECAUTIONS, Renal).

Saxagliptin

Of the total number of subjects (N=4148) studied in controlled clinical safety and efficacy studies of saxagliptin, 634 (15.3%) patients were 65 years and over, of which 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, metformin should only be used in patients with normal renal function (see CONTRAINDICATIONS).

Monitoring and Laboratory Tests

Response should be monitored by periodic measurements of blood glucose and HbA1C levels.

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) should be performed regularly. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, Vitamin B_{12} deficiency should be excluded.

Patients with a history of heart failure or other risk factors for heart failure, including renal impairment, should be closely monitored for signs and symptoms of heart failure.

Monitoring of renal function:

Before initiation of KOMBOGLYZE therapy, and periodically thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated and in the elderly, renal function should be assessed more frequently and KOMBOGLYZE discontinued if evidence of renal impairment is present.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Saxagliptin

In a placebo-controlled clinical study of patients receiving saxagliptin 5 mg or placebo as an add-on to metformin, the incidence of serious adverse events was 9.9% and 5.6% respectively. The most commonly reported adverse events, regardless of causality and more common with saxagliptin than placebo, were nasopharyngitis and bronchitis. Discontinuation of therapy due to adverse events occurred in 7.3% and 4.5% of patients, respectively.

In a placebo-controlled clinical study of patients receiving saxagliptin 5 mg or placebo as an add-on to metformin and a sulfonylurea, the incidence of serious adverse events was 2.3% and 5.5%, respectively. The most commonly reported adverse events, reported regardless of causality and more common with saxagliptin than placebo, were hypoglycemia, hypertension and diarrhea. Discontinuation of therapy due to adverse events occurred in 0.8 % and 2.3% of patients, respectively.

In a placebo-controlled clinical study of patients receiving saxagliptin 5 mg or placebo as an add-on to insulin (with or without metformin), the incidence of serious adverse events was 8.2% and 8.6% respectively. The most commonly reported adverse events, reported regardless of causality and more common with saxagliptin than placebo, were headache and bronchitis. Discontinuation of therapy due to adverse events occurred in 3.0% and 2.0% of patients, respectively.

Metformin hydrochloride

The adverse events most commonly associated with metformin (saxagliptin/metformin) are diarrhea, nausea, and upset stomach.

Lactic acidosis: very rare, but serious side effect (<1/10, 000 and isolated reports). Lactic acidosis is fatal in approximately 50% of cases (see WARNINGS AND PRECAUTIONS, and OVERDOSAGE).

Gastrointestinal Reactions: very common: (>1/10) Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin monotherapy than in placebo-treated patients, particularly during initiation of metformin therapy. These symptoms are generally transient and resolve spontaneously during continued treatment.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take metformin (metformin HCl) with meals (see DOSAGE and ADMINISTRATION).

Because significant diarrhea and/or vomiting can cause dehydration and prerenal azotemia, metformin should be temporarily discontinued, under such circumstances.

For patients who have been stabilized on metformin, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: common (≥1/100): During initiation of metformin therapy complaints of taste disturbance are common, i.e. metallic taste.

Dermatologic Reactions: very rare (<1/10,000 and isolated reports): The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for metformin monotherapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

Hematologic: During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin monotherapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. Five cases of megaloblastic anemia have been reported with metformin administration and no increased incidence of neuropathy has been observed. (See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin is rare (≥1/10,000 and <1/1,000). Consideration of such aetiology is recommended if a patient presents with megaloblastic anemia.

Hepatic: very rare (<1/10,000 and isolated reports): Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events, reported regardless of causality assessment, in ≥ 2 % of patients treated with either saxagliptin 5 mg or placebo as an add-on to metformin are shown in Table 1.

Table 1 Adverse Events (Regardless of Investigator Assessment of Causality) in the Add-on to Metformin[a] Study (24-week Short Term Study and the Long Term Extension) Reported in ≥ 2% of Patients Treated with Either Saxagliptin 5 mg + Metformin or Metformin + Placebo

	Number of Patients (%)	
Body system/Organ Class Adverse Event	**Saxagliptin 5 mg + Metformin N=191**	**Metformin + Placebo N=179**
Blood and lymphatic system disorders		
Anemia	11 (5.8)	3 (1.7)
Eosinophilia	6 (3.1)	0
Cardiac disorders		
Coronary artery disease	4 (2.1)	0
Gastrointestinal disorders		
Diarrhea	14 (7.3)	23 (12.8)
Dyspepsia	11 (5.8)	8 (4.5)
Toothache	8 (4.2)	11 (6.1)
Abdominal pain	7 (3.7)	2 (1.1)
Abdominal pain upper	7 (3.7)	5 (2.8)
Nausea	7 (3.7)	8 (4.5)
Vomiting	7 (3.7)	7 (3.9)
Constipation	5 (2.6)	3 (1.7)
Gastroesophageal reflux disease	4 (2.1)	1 (0.6)
Gastritis	2 (1.0)	2 (1.1)
General disorders and administration site conditions		
Edema peripheral	11 (5.8)	9 (5.0)
Chest pain	5 (2.6)	2 (1.1)
Fatigue	5 (2.6)	7 (3.9)
Asthenia	0	2 (1.1)
Infections and infestations		
Influenza	22 (11.5)	23 (12.8)
Nasopharyngitis	21 (11.0)	19 (10.6)
Bronchitis	18 (9.4)	11 (6.1)
Upper respiratory tract infection	17 (8.9)	14 (7.8)
Urinary tract infection	15 (7.9)	12 (6.7)
Sinusitis	10 (5.2)	9 (5.0)
Gastroenteritis	5 (2.6)	3 (1.7)
Tooth infection	5 (2.6)	3 (1.7)
Gastroenteritis viral	4 (2.1)	2 (1.1)
Pharyngitis	2 (1.0)	4 (2.2)

	Number of Patients (%)	
Body system/Organ Class Adverse Event	**Saxagliptin 5 mg + Metformin N=191**	**Metformin + Placebo N=179**
Viral infection	1 (0.5)	4 (2.2)
Pharyngotonsillitis	1 (0.5)	1 (0.6)
Injury, poisoning, and procedural complications		
Limb Injury	3 (1.6)	1 (0.6)
Investigations		
Blood creatine phosphokinase increased	4 (2.1)	2 (1.1)
Alanine aminotransferase increased	1 (0.5)	4 (2.2)
Metabolism and nutrition disorders		
Hypoglycemia [b]	17 (8.9)	18 (10.1)
Hypertriglyceridemia	6 (3.1)	2 (1.1)
Dyslipidemia	3 (1.6)	4 (2.2)
Musculoskeletal and connective tissue disorders		
Arthralgia	16 (8.4)	9 (5.0)
Back pain	15 (7.9)	16 (8.9)
Osteoarthritis	8 (4.2)	4 (2.2)
Myalgia	6 (3.1)	4 (2.2)
Pain in extremity	6 (3.1)	13 (7.3)
Exostosis	4 (2.1)	2 (1.1)
Musculoskeletal pain	4 (2.1)	9 (5.0)
Muscle spasms	3 (1.6)	4 (2.2)
Nervous system disorders		
Headache	17 (8.9)	20 (11.2)
Dizziness	8 (4.2)	9 (5.0)
Parasthesia	0	2 (1.1)
Psychiatric disorders		
Anxiety	8 (4.2)	5 (2.8)
Depression	6 (3.1)	4 (2.2)
Renal and urinary disorders		
Microalbuminuria	5 (2.6)	4 (2.2)
Nephrolithiasis	4 (2.1)	3 (1.7)
Dysuria	0	4 (2.2)
Respiratory, thoracic, and mediastinal disorders		
Cough	7 (3.7)	9 (5.0)
Pharyngolaryngeal pain	5 (2.6)	3 (1.7)
Skin and subcutaneous tissue disorders		
Rash	6 (3.1)	5 (2.8)
Alopecia	4 (2.1)	0
Pruritus	3 (1.6)	1 (0.6)
Vascular disorders		
Hypertension	9 (4.7)	12 (6.7)

[a] The mean duration of exposure to double-blind study medication, including exposure after the initiation of rescue medication, was 75 weeks (Standard Deviation = 34) for saxagliptin 5 mg plus metformin and 68 weeks (Standard Deviation = 35) for placebo plus metformin groups.
[b] "Hypoglycemia" includes events of Hypoglycemia and Blood Glucose Decreased.

Rash-related adverse events in the add-on to metformin study (24-week short-term and long-term extension) were reported in 4.2% and 2.8% of patients who received saxagliptin 5 mg and placebo, respectively.

In a pooled analysis of the 24-week placebo-controlled clinical trials, hypersensitivity-related events, such as urticaria and facial edema were reported in 1.5% and 0.4% of patients who received saxagliptin 5 mg and placebo, respectively. None of these events in patients who received saxagliptin required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Adverse reactions, reported regardless of causality assessment, in ≥ 2 % of patients treated with either saxagliptin 5 mg or placebo as an add-on to metformin and a sulfonylurea are shown in Table 2.

Table 2 Adverse Reactions (Regardless of Investigator Assessment of Causality) in the Add-on to Meformin and a Sulfonylurea (SU) Study[a] (24-week) Reported in ≥ 2% of Patients Treated with Either Saxagliptin 5 mg or Placebo

	Number of Patients (%) Add-on to Metformin and SU	
Body System/Organ Class Adverse Event	**Saxagliptin 5 mg + Metformin + SU N=129**	**Placebo + Metformin + SU N=128**
Blood and lymphatic system disorders		
Anemia	1 (0.8)	5 (3.9)
Gastrointestinal disorders		
Diarrhea	7 (5.4)	5 (3.9)
Flatulence	4 (3.1)	0
Gastritis	3 (2.3)	3 (2.3)
Nausea	2 (1.6)	4 (3.1)
Constipation	1 (0.8)	3 (2.3)
Infections and infestations		
Nasopharyngitis	8 (6.2)	12 (9.4)
Upper respiratory tract infection	6 (4.7)	6 (4.7)
Urinary tract infection	4 (3.1)	8 (6.3)
Pharyngitis	0	3 (2.3)
Oral candidiasis	0	3 (2.3)
Metabolism and nutrition disorders		
Hypoglycemia[b]	13 (10.1)	8 (6.3)

	Number of Patients (%) Add-on to Metformin and SU	
Body System/Organ Class Adverse Event	**Saxagliptin 5 mg + Metformin + SU N=129**	**Placebo + Metformin + SU N=128**
Dyslipidemia	5 (3.9)	7 (5.5)
Hyperglycemia	4 (3.1)	4 (3.1)
Musculoskeletal and connective tissue disorders		
Pain in extremity	2 (1.6)	4 (3.1)
Arthralgia	2 (1.6)	3 (2.3)
Back pain	1 (0.8)	4 (3.1)
Nervous system disorders		
Headache	4 (3.1)	3 (2.3)
Dizziness	3 (2.3)	2 (1.6)
Neuropathy peripheral	3 (2.3)	0
Psychiatric Disorders		
Insomnia	0	3 (2.3)
Respiratory, thoracic, and mediastinal disorders		
Cough	4 (3.1)	1 (0.8)
Skin and subcutaneous tissue disorders		
Rash	2 (1.6)	3 (2.3)
Vascular disorders		
Hypertension	7 (5.4)	2 (1.6)

[a] The mean duration of exposure to double-blind study medication was 159 days (Standard Deviation = 31) in the saxagliptin 5 mg group and 160 days (Standard Deviation = 30) for the placebo group.
[b] "Hypoglycemia" includes events of Hypoglycemia and Blood Glucose Decrease.

Adverse reactions, reported regardless of causality assessment, in ≥ 2 % of patients treated with either saxagliptin 5 mg or placebo as an add-on to insulin (with or without metformin) are shown in Table 3.

Table 3 Adverse Reactions (Regardless of Investigator Assessment of Causality) in the Add-on to Insulin Study[a] (24-week Short Term Study and the Long Term Extension) Reported in ≥ 2% of Patients Treated with Either Saxagliptin 5 mg or Placebo

	Number of Patients (%) Add-on to Insulin (with or without Metformin)	
Body System/Organ Class Adverse Event	**Saxagliptin 5 mg + Insulin N=304**	**Placebo + Insulin N=151**
Blood and lymphatic system disorders		
Anemia	6 (2.0)	4 (2.6)

	Number of Patients (%) Add-on to Insulin (with or without Metformin)	
Body System/Organ Class Adverse Event	**Saxagliptin 5 mg + Insulin N=304**	**Placebo + Insulin N=151**
Gastrointestinal disorders		
Diarrhea	14 (4.6)	7 (4.6)
Constipation	12 (3.9)	5 (3.3)
Abdominal pain	8 (2.6)	2 (1.3)
Gastritis	8 (2.6)	2 (1.3)
Nausea	5 (1.6)	5 (3.3)
General disorders and administration site conditions		
Edema peripheral	9 (3.0)	5 (3.3)
Infections and infestations		
Urinary tract infection	24 (7.9)	12 (7.9)
Nasopharyngitis	19 (6.3)	10 (6.6)
Upper respiratory tract infection	19 (6.3)	11 (7.3)
Bronchitis	16 (5.3)	5 (3.3)
Pharyngitis	11 (3.6)	8 (5.3)
Influenza	10 (3.3)	14 (9.3)
Cystitis	8 (2.6)	3 (2.0)
Gastroenteritis	7 (2.3)	2 (1.3)
Investigations		
Blood creatine phosphokinase increased	7 (2.3)	1 (0.7)
Metabolism and nutrition disorders		
Hypoglycemia[b]	69 (22.7)	40 (26.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (4.3)	5 (3.3)
Back pain	10 (3.3)	6 (4.0)
Osteoarthritis	7 (2.3)	0
Pain in extremity	7 (2.3)	10 (6.6)
Musculoskeletal pain	3 (1.0)	6 (4.0)
Nervous system disorders		
Headache	18 (5.9)	6 (4.0)
Dizziness	8 (2.6)	3 (2.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	7 (2.3)	6 (4.0)
Vascular disorders		
Hypertension	9 (3.0)	8 (5.3)
Hypertensive crisis[c]	6 (2.0)	1 (0.7)

[a]The mean duration of exposure to double-blind study medication, including exposure after changes in insulin medication, was 47 week (Standard Deviation = 13) for saxagliptin 5 mg plus insulin and 47 weeks (Standard Deviation = 13) for placebo plus insulin groups.
[b]"Hypoglycemia" includes events of Hypoglycemia and Blood Glucose Decreased.

[c]Term as reported; cases do not meet medically accepted definition of hypertensive crisis.

In the short-term 24-week add-on to insulin study, the overall incidence of reported hypoglycemia was 18.4% for saxagliptin 5 mg and 19.9% for placebo. The incidence of confirmed hypoglycemic events, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤ 2.8 mmol/L, was 5.3% for the saxagliptin 5 mg treated group versus 3.3% for the placebo group. In the long-term extension of the add-on to insulin study, the overall incidence of hypoglycemia was lower for saxagliptin 5 mg (22.7%) versus placebo (26.5%) plus insulin with or without metformin.

Serious Adverse Reactions (reported in < 2% of patients) and Adverse Reactions of Interest* (reported in < 2% of patients and in at least 2 patients), Regardless of Investigator Assessment of Causality and Frequency > Placebo, in the Add-on to Metformin, Add-on to Metformin and a Sulfonylurea Study (24-week) and Add-on to Insulin (with or without Metformin) Studies (24-week short-term and the long-term extensions)

* System Organ Classes were considered to be of interest based on the adverse event profile of the DPP-4 inhibitor class of drugs, non-clinical data for saxagliptin, as well as the patient population.

Blood and lymphatic system disorders*: lymphopenia
Gastrointestinal disorders: abdominal pain, diarrhea, vomiting
Hepatobiliary disorders: cholecystitis, hepatitis
Immune system disorders*: sarcoidosis, hypersensitivity
Infections and infestations: clostridium difficile colitis, urosepsis, diverticulitis, lower respiratory tract infection
Injury, poisoning and procedural complications: road traffic accident, ankle fracture, fall, incisional hernia, limb injury, skin laceration
Investigations*: blood cholesterol increased, lymphocyte count decreased
Metabolism and nutrition disorders: dehydration
Musculoskeletal and connective tissue disorders: arthralgia, osteoarthritis
Neoplasms benign, malignant and unspecified (including cysts and polyps): pancreatic cancer, laryngeal cancer
Nervous system disorders: altered state of consciousness, dizziness
Renal and urinary disorders: calculus ureteric, calculus urinary, renal impairment
Respiratory, thoracic and mediastinal disorders: pulmonary embolism
Skin and subcutaneous tissue disorders*: rash papular, pruritus, skin lesion, hyperhidrosis
Surgical and medical procedures: sterilisation

Abnormal Hematologic and Clinical Chemistry Findings

Saxagliptin

Absolute Lymphocyte Counts: A dose-related mean decrease in absolute lymphocyte count was observed with saxagliptin. From a baseline absolute lymphocyte count of approximately 2200 cells/µL, a mean decrease of approximately 100 cells/µL relative to placebo was observed in a pooled analysis of the placebo-controlled clinical studies.

Mean absolute lymphocyte counts remained stable and within the normal limits with daily dosing up to 102 weeks in duration.

The proportion of patients who were reported to have a lymphocyte count ≤ 750 cells/ μL was 1.5% in the saxagliptin 5 mg group and 0.4% in the placebo group. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of saxagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g. human immunodeficiency virus) is unknown.

Platelets: saxagliptin did not demonstrate a clinically meaningful or consistent effect on platelet count in the double-blind, controlled clinical safety and efficacy trials. In the add-on to insulin trial, there was a -2.6% decrease from baseline in platelet count in the saxagliptin group compared with a -0.1% decrease in the placebo group. An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to saxagliptin is not known.

Urinary white and red blood cell counts: In the add-on to insulin trial, there was a higher percentage of saxagliptin patients, compared to placebo patients who presented with marked urinary red blood cell counts (15.1% saxagliptin versus 3.2% placebo) and urinary white blood cell counts (30.4% versus 18.9%). No consistent findings of urine laboratory abnormalities have been observed in the overall saxagliptin clinical program. No imbalances were observed for either URBC or UWBC in the pooled analysis of Phase 2/3 studies.

Metformin hydrochloride

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions

Saxagliptin

Additional adverse reactions have been identified during post-marketing use of saxagliptin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura

Gastrointestinal disorders: acute and chronic pancreatitis (see WARNINGS AND PRECAUTIONS)

Immune system disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, urticaria and exfoliative skin conditions, including Stevens-Johnson syndrome (see

CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions)

Musculoskeletal and connective tissue disorders: severe and disabling arthralgia (see WARNINGS AND PRECAUTIONS, Musculoskeletal and connective tissue disorders)

Skin and subcutaneous tissue disorders: bullous pemphigoid

Post-Marketing, Cardiovascular Safety

Saxagliptin

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial was a CV outcome trial in 16,492 type 2 diabetic patients (median HbA1c = 7.6%) (12959 with established CV disease; 3533 with multiple risk factors only) who were randomized to ONGLYZA (n=8280) or placebo (n=8212). The study population also included those ≥65 years (n=8561) and ≥ 75 years (n=2330), with normal or mild renal impairment (n=13,916) as well as moderate (n=2240) or severe (n=336) renal impairment. Subjects were followed for a mean duration of 2 years.

The primary 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 ischemic stroke.

The trial established that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the primary composite endpoint observed with saxagliptin to that observed in the placebo group was <1.3. The study did not demonstrate the superiority of saxagliptin compared with placebo when added to current background therapy, in reducing the primary MACE endpoint (HR 1.00; 95% CI: 0.89, 1.12; p = 0.986).

Hospitalization for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%) [HR = 1.27; (95% CI 1.07, 1.51). Subjects on saxagliptin with a baseline history of congestive heart failure, especially those who also had renal impairment and/or MI, were at higher absolute risk for hospitalization for heart failure.

DRUG INTERACTIONS

Overview

Saxagliptin and Metformin hydrochloride

Pharmacokinetic drug interaction studies with KOMBOGLYZE (saxagliptin/metformin hydrochloride) have not been performed; however, such studies have been conducted with the individual components of KOMBOGLYZE.

Saxagliptin

The metabolism of saxagliptin is primarily mediated by P450 3A4/5 (CYP3A4/5).

In *in vitro* studies, saxagliptin and its major pharmacologically active metabolite neither inhibited nor induced CYP3A4. In addition, in *in vitro* studies, saxagliptin and its major pharmacologically active metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, nor induced CYP1A2, 2B6, 2C9. Therefore, saxagliptin is unlikely to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is neither a significant inhibitor of P-glycoprotein (P-gp) nor an inducer of P-gp, and is unlikely to cause interactions with drugs that utilize these pathways.

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.

Metformin hydrochloride

In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin 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 sulfonylureas, which are extensively bound to serum proteins.

Drug-Drug Interactions

Saxagliptin

Effect of other drugs on saxagliptin

In studies conducted in healthy subjects as described below, the pharmacokinetics of saxagliptin and its major metabolite were not meaningfully altered by metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole, omeprazole, aluminum hydroxide + magnesium hydroxide + simethicone combination, or famotidine. These drugs are considered unlikely to cause a clinically meaningful interaction with saxagliptin.

CYP3A4/5 Inducers: The coadministration of saxagliptin and CYP3A4/5 inducers, other than rifampin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) have not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metabolite. Glycemic control should be carefully assessed when saxagliptin is used concomitantly with a potent CYP3A4 inducer.

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an OCT-1 and OCT-2 substrate, decreased the C_{max} of saxagliptin by 21%; however, the AUC was unchanged. Therefore, metformin is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other OCT-1 and OCT-2 substrates would not be expected.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, did not affect the pharmacokinetics of saxagliptin. Therefore, glyburide is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other CYP2C9 substrates would not be expected.

Pioglitazone*:* Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of saxagliptin. Therefore, pioglitazone is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other CYP2C8 substrates would not be expected.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of saxagliptin. Therefore, digoxin is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other P-gp substrates would not be expected.

Simvastatin*:* Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, increased the C_{max} of saxagliptin by 21%; however, the AUC of saxagliptin was unchanged. Therefore, simvastatin is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin would not be expected with other substrates of CYP3A4/5.

Diltiazem: Coadministration of a single dose of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the C_{max} and AUC for saxagliptin by 63% and 109%, respectively. This coadministration was also associated with 44% and 34% decreases in C_{max} and AUC(INF) values, respectively of its major metabolite. Therefore, diltiazem is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other moderate CYP3A4/5 inhibitors would not be expected.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and ketoconazole (200 mg every 12 hours at steady state), a potent inhibitor of CYP3A4/5 and P-gp, increased the C_{max} and AUC for saxagliptin by 62% and 145 % respectively. This coadministration was also associated with 95% and 88% decreases in C_{max} and AUC(INF) values, respectively of its major metabolite.

Following coadministration of a single dose of saxagliptin at 20 times the recommended dose (100 mg) with ketoconazole, transient flu-like symptoms and a transient decrease in absolute lymphocyte count were observed. Additionally, transient decreases in absolute lymphocyte count were observed without any flu-like symptoms following coadministration of a single dose of saxagliptin at 4 times the recommended dose (20 mg) with ketoconazole.

Rifampin (Rifampicin): Coadministration of a single dose of saxagliptin (5 mg) with the potent CYP3A4/5 and P-gp inducer rifampin (600 mg once daily at steady state), decreased the C_{max} and AUC of saxagliptin by 53% and 76%, respectively. There was a corresponding increase in C_{max} (39%) but no significant change in plasma AUC of the active metabolite. There was no change in the maximum DPP4 inhibition (%Imax) and only a 6% decrease in the mean area under the effect time curve for DPP4 inhibition (AUEC) over a 24-hour period (the dosing interval for saxagliptin) when saxagliptin was coadministered with rifampin; however, a shorter DPP4 inhibition T-HALF was observed during the rifampin coadministration period (25.9 hours for saxagliptin-alone versus 14.5 hours for saxagliptin

plus rifampin). See also WARNINGS AND PRECAUTIONS, Use with Potent CYP 3A4 Inducers.

Omeprazole: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and omeprazole (40 mg), a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3, did not alter the pharmacokinetics of saxagliptin. Therefore, omeprazole is considered unlikely to cause a clinically meaningful interaction with saxagliptin. Meaningful interactions of saxagliptin with other CYP2C19 inhibitors or MRP-3 inducers would not be expected.

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

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

Effect of saxagliptin on other drugs

In studies conducted in healthy subjects, as described below, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole or active components of an estrogen/progestin combined oral contraceptive. Saxagliptin is considered unlikely to cause a clinically meaningful interaction with these drugs.

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an OCT-1 and OCT-2 substrate, did not alter the pharmacokinetics of metformin in healthy subjects. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with metformin. Saxagliptin is not an inhibitor of OCT-1 and OCT-2- mediated transport.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, increased the plasma C_{max} of glyburide by 16%; however, the AUC of glyburide was unchanged. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with glyburide. saxagliptin does not meaningfully inhibit CYP2C9-mediated metabolism.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 substrate, increased the plasma C_{max} of pioglitazone by 14%; however, the AUC of pioglitazone was unchanged. Therefore, saxagliptin is considered

unlikely to cause a clinically meaningful interaction with pioglitazone. Saxagliptin does not meaningfully inhibit or induce CYP2C8-mediated metabolism.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of digoxin. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with digoxin. Saxagliptin is not an inhibitor or inducer of P-gp-mediated transport.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, did not alter the pharmacokinetics of simvastatin. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with simvastatin. Saxagliptin is not an inhibitor or inducer of CYP3A4/5-mediated metabolism.

Diltiazem: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the plasma C_{max} of diltiazem by 16%;. however, the AUC of diltiazem was unchanged. Therefore, saxagliptin is considered unlikely to cause a clinically meaningful interaction with diltiazem.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and multiple doses of ketoconazole (200 mg every 12 hours at steady state), a potent inhibitor of CYP3A4/5 and P-gp, decreased the geometric means for C_{max} and AUC(INF) of ketoconazole by 16 % and by 13% respectively, relative to those observed following administration of 200 mg ketoconazole q 12 h alone.

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

Metformin hydrochloride

Glyburide: In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and Cmax were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by

coadministration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

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

Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. 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 KOMBOGLYZE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Anticoagulant: Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Therefore, patients receiving phenprocoumon or other antivitamin K anticoagulants should be monitored carefully when both types of drugs are used simultaneously. In such cases, an important increase of prothrombin time may occur upon cessation of KOMBOGLYZE therapy, with an increased risk of hemorrhage.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid and beta-2-agonists. ACE inhibitors may decrease the blood glucose levels. When such drugs are administered to a patient receiving KOMBOGLYZE the patient should be closely observed to maintain adequate glycemic control.

Drug-Food Interactions

There are no known interactions with food. Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism may give rise to modest increases in plasma levels of saxagliptin.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Drug-Lifestyle Interactions

No studies of the effects of KOMBOGLYZE on the ability to drive and use machines have been performed. KOMBOGLYZE is not expected to affect the ability to drive and use machines under usual circumstances.

The effect of smoking and alcohol on the pharmacokinetics of KOMBOGLYZE have not been specifically studied.

Metformin hydrochloride

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving KOMBOGLYZE (see CONTRAINDICATIONS AND WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Recommended Dose and Dosage Adjustment

The dosage of antihyperglycemic therapy with KOMBOGLYZE (saxagliptin/metformin hydrochloride) should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 5 mg saxagliptin and 2000 mg metformin.

The dose of KOMBOGLYZE should be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin.

The following dosage strengths are available:

2.5 mg saxagliptin/500 mg metformin hydrochloride

2.5 mg saxagliptin/850 mg metformin hydrochloride

2.5 mg saxagliptin/1000 mg metformin hydrochloride

Patients inadequately controlled on a maximally tolerated dose of metformin monotherapy: For patients inadequately controlled on metformin alone, the usual starting dose of KOMBOGLYZE should provide saxagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) plus the dose of metformin already being taken.

Patients switching from coadministration of saxagliptin and metformin: For patients switching from saxagliptin coadministrated with metformin, KOMBOGLYZE may be initiated at the dose of saxagliptin and metformin already being taken.

Renal Impairment: Use of KOMBOGLYZE is contraindicated in patients with renal impairment (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis).

Hepatic Impairment: Use of KOMBOGLYZE in moderate to severe hepatic impairment is contraindicated. Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, KOMBOGLYZE is not recommended in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS).

Pediatrics (<18 years of age): Safety and effectiveness of KOMBOGLYZE in pediatric patients have not been established. Therefore, KOMBOGLYZE should not be used in this patient population.

Geriatrics (≥65 years of age): Since saxagliptin and metformin are eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, KOMBOGLYZE should be used with caution as age increases (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis and ACTION AND CLINICAL PHARMACOLOGY, Geriatrics).

Missed Dose

If a dose of KOMBOGLYZE is missed, the patient should wait for the next dose at the usual time. A double dose of KOMBOGLYZE should not be taken on the same day.

OVERDOSAGE

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite are removed by hemodialysis (23% of dose over 4 hours). 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 hemodialysis. Events of hypoglycemia have been reported with overdoses of metformin, although a causal association has not been established.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

KOMBOGLYZE (saxagliptin/metformin hydrochloride)

KOMBOGLYZE combines two antihyperglycemic agents with complementary mechanisms of action to improve both fasting plasma glucose and postprandial plasma glucose in patients with type 2 diabetes: saxagliptin hydrochloride, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class. KOMBOGLYZE targets three core defects of type 2 diabetes which are: decreased insulin synthesis and release, increased hepatic glucose production and decreased insulin sensitivity.

Saxagliptin

Saxagliptin is a potent, selective, reversible, competitive, DPP-4 inhibitor. Saxagliptin demonstrates selectivity for DPP-4 versus other DPP enzymes, including 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.

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.

The concentration of GLP-1 is 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 postprandial insulin release and decreases postprandial glucagon concentrations in the circulation in a glucose-dependent manner.

In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels may lead to lower hemoglobin A1C (HbA1C) and lower fasting and postprandial glucose concentrations.

Metformin hydrochloride

Metformin is an antihyperglycemic 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 utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal

subjects (except in special circumstances, see WARNINGS AND PRECAUTIONS, Hypoglycemia) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamics

Saxagliptin

In patients with type 2 diabetes, administration of saxagliptin led to dose-dependent 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 postprandial glucagon concentrations, and increased glucose-dependent beta cell responsiveness with higher postprandial insulin and C-peptide concentrations. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac electrophysiology: In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study, 40 healthy subjects were administered saxagliptin 40 mg (8 times the RHD), saxagliptin 10 mg (2 times the RHD), or placebo once daily for 4 days, or a single dose of moxifloxacin 400 mg as a positive control. The saxagliptin 10 mg and 40 mg treatments were not associated with any prolongation of the QTc, QRS, or PR intervals. In the saxagliptin 10 mg treatment a significant increase in heart rate was observed at 0.5, 1, 1.5, 4, and 12 h post-dosing, with a maximum placebo- and baseline-corrected mean increase of 3.75 (90% 1.55, 5.95) beats per minute at 0.5 post-dosing when the baseline-corrected change in the placebo treatment at this time was -1.4 (90% CI -3.0, 0.1) beats per minute. Significant increases in heart rate were also observed in the saxagliptin 40 mg treatment at 0.5, 4, and 12 hours post-dosing, with a maximum placebo- and baseline-corrected mean increase of 4.5 (90% CI 2.23, 6.82) beats per minute at 4 hours post-dose dose when the baseline-corrected change in the placebo treatment at this time was -3.3 (90% CI -5.0, -1.6) beats per minute. The effect of the recommended 5 mg dose was not investigated in this study.

Pharmacokinetics

In a bioequivalence study of KOMBOGLYZE 2.5/500 (mg/mg saxagliptin/metformin hydrochloride), both the saxagliptin component and the metformin component were bioequivalent to coadministered 2.5 mg saxagliptin and 500 mg metformin hydrochloride tablets under fed and fasted conditions in healthy subjects (see Table 4).

The KOMBOGLYZE dosage formats (i.e. 2.5/500, 2.5/850 and 2.5/1000 saxagliptin/metformin hydrochloride) are proportionally formulated.

Table 4 **Geometric Mean Pharmacokinetic Parameters for Saxagliptin and Metformin Following Single Oral Dose of KOMBOGLYZE or Coadministration of Corresponding Doses of Saxagliptin and Metformin as Individual Tablets to Healthy Subjects Under Fasted and Fed Conditions**

Saxagliptin				
Treatment	**N**	**$AUC_{(0-t)}$ (ng·h/mL)**	**$AUC_{(0-\infty)}$ (ng·h/mL)**	**C_{max} (ng/mL)**
A	27	50.28	52.17	10.54
B	26	51.60	53.73	11.53
C	26	59.00	61.31	12.71
D	26	58.94	60.88	12.79
Metformin				
Treatment	**N**	**$AUC_{(0-t)}$ (ng·h/mL)**	**$AUC_{(0-\infty)}$* (ng·h/mL)**	**C_{max} (ng/mL)**
A	27	8035	8143	1058
B	26	7906	8070	1045
C	26	7498	7613	810
D	26	7654	7691	812

Treatment A: 2.5-mg saxagliptin and 500 mg metformin hydrochloride tablets administered together in the fasted state.
Treatment B: KOMBOGLYZE saxagliptin (2.5 mg) /metformin hydrochloride (500mg) administered in the fasted state.
Treatment C: 2.5-mg saxagliptin and 500 mg metformin hydrochloride tablets administered together in the fed state.
Treatment D: KOMBOGLYZE saxagliptin (2.5 mg) /metformin hydrochloride (500mg) administered in the fed state.
*The number of individual metformin $AUC_{(0-\infty)}$ values reported was 26 for Treatments A and B and 25 for Treatments C and D.

Absorption:

Saxagliptin

The amount of saxagliptin absorbed following an oral dose is at least 75%. Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with a high-fat meal resulted in no change in saxagliptin C_{max} and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach C_{max} (T_{max}) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

Metformin hydrochloride

After an oral dose of metformin, T_{max} is reached in 2.5 hours. The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-

60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

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

Distribution:

Saxagliptin

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

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 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 selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

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) nor 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 feces 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.

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- and 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.

Metformin hydrochloride

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans).

Special Populations and Conditions

Pediatrics (< 18 years of age):

Saxagliptin

Pharmacokinetics in the pediatric population have not been studied. Therefore, KOMBOGLYZE should not be used in this patient population.

Geriatrics (≥ 65 years of age):

Saxagliptin

No dosage adjustment is necessary 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.

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 Cmax 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. (See DOSAGE AND ADMINISTRATION, Geriatrics, WARNINGS AND PRECAUTIONS, Geriatrics.).

KOMBOGLYZE treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis).

Gender: No dosage adjustment is necessary based on gender.

Saxagliptin

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 the clinical relevance of this difference is unknown.

Metformin hydrochloride

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

Race: No dosage adjustment is necessary based on race.

Saxagliptin

An exposure modeling analysis compared the pharmacokinetics of saxagliptin and its major metabolite in 309 white subjects with 105 non-white subjects (consisting of 6 race 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 antihyperglycemic 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).

Renal Impairment:

KOMBOGLYZE should not be used in patients with renal impairment (see CONTRAINDICATIONS).

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 Cmax of saxagliptin or its major metabolite. In subjects with mild renal impairment, the AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than AUC values in subjects with normal renal function.

In subjects with moderate or severe renal impairment or in subjects with ESRD on hemodialysis, 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. A dose of 2.5 mg once daily is needed in patients with moderate and severe renal impairment. Therefore use of KOMBOGLYZE in this population is not recommended.

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance (< 60 mL/min)), the plasma and blood half-life of metformin are prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment:

Use of KOMBOGLYZE in moderate to severe hepatic impairment is contraindicated. KOMBOGLYZE is not recommended in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS).

Saxagliptin

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. Use in moderate to severe hepatic impairment is not recommended.

Metformin hydrochloride

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

STORAGE AND STABILITY

Temperature: Store at room temperature (15-25°C).

Others: Keep in a safe place out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

KOMBOGLYZE (saxagliptin/metformin hydrochloride) is available for oral administration as immediate release tablets containing saxagliptin as saxagliptin hydrochloride and metformin hydrochloride in the following formats:

KOMBOGLYZE (saxagliptin/metformin hydrochloride) 2.5mg/500mg tablets are pink, biconvex, round, film-coated tablets with "2.5/500" printed on one side and "4245" printed on the reverse side, in blue ink. They are supplied in blisters of 10 X 6 tablets.

KOMBOGLYZE (saxagliptin/metformin hydrochloride) 2.5mg/850mg tablets are light brown to brown, biconvex, round, film-coated tablets with "2.5/850" printed on one side and "4246" printed on the reverse side, in blue ink. They are supplied in blisters of 10 X 6 tablets.

KOMBOGLYZE (saxagliptin/metformin hydrochloride) 2.5mg/1000mg tablets are pale yellow to light yellow, biconvex, oval shaped, film-coated tablets with "2.5/1000" printed on one side and "4247" printed on the reverse side, in blue ink. They are supplied in blisters of 10 X 6 tablets.

Information for the patient is provided as a package insert in the KOMBOGLYZE packages.

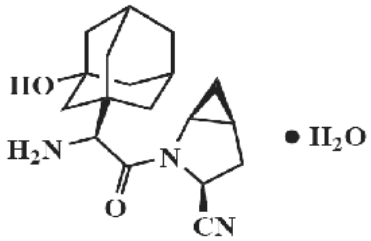
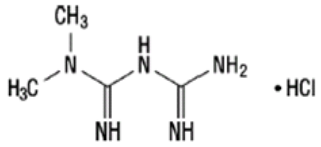
Composition

KOMBOGLYZE tablets contain the following non-medicinal ingredients: magnesium stearate and povidone. In addition, the film coatings contain the following inactive ingredients: polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc, and red iron oxide (2.5mg/500mg strength) or yellow iron oxide (2.5mg/1000mg strength) or a combination of red and yellow iron oxides (2.5mg/850mg strength).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	saxagliptin monohydrate[a]	metformin hydrochloride
Chemical Name:	2-azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2*S*)-2-amino-2-(3-hydroxytricyclo[3.3.1.1]dec-1-yl)acetyl]-, hydrate (1:1), (1*S*,3*S*,5*S*)- or (1*S*,3*S*,5*S*)-2-[(2*S*)-amino(3-hydroxytricyclo[3.3.1.1]dec-1-yl)acetyl]-2- azabicyclo[3.1.0]hexane-3-carbonitrile monohydrate	N,N-dimethyl biguanide hydrochloride or N,N-dimethylimidodicarbonimidic diamide hydrochloride
Molecular Formula and Molecular Mass:	$C_{18}H_{25}N_3O_2 \cdot H_2O$ 333.43; (315.41 anhydrous)	$C_4H_{11}N_5 \cdot HCl$ 165.63
Structural Formula:		
Physicochemical Properties:	Saxagliptin, in the free base monohydrate form, is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).	Metformin hydrochloride is a white to off-white crystalline compound. It 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.

[a]saxagliptin monohydrate is converted to saxagliptin hydrochloride *in-situ* during drug product manufacturing

CLINICAL TRIALS

There have been no clinical efficacy studies conducted with KOMBOGLYZE (saxagliptin/metformin hydrochloride) tablets; however, bioequivalence of KOMBOGLYZE tablets with coadministered saxagliptin and metformin hydrochloride immediate release tablets was demonstrated (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

The combination of saxagliptin and metformin has been evaluated for safety and efficacy in a double-blind, placebo-controlled study in patients with type 2 diabetes mellitus (see Table 5).

Study demographics and trial design

Table 5 Summary of patient demographics for clinical trials in specific indication

Trial design	Dosage, route of administration and duration	Study subjects per treatment arm Subjects ≥ 65 years of age Subjects ≥ 75 years of age (N=number)	Mean age (Range)	Gender (% M/F)
Add-on Combination Therapy with Metformin				
Multicentre, randomized, double-blind, placebo-controlled	open-label metformin (1500 – 2500 mg) plus saxagliptin 5 mg qd or placebo Oral, 24 weeks	Saxagliptin 5 mg N=191 ≥ 65 years N=32 ≥ 75 years N=2 Placebo N= 179 ≥ 65 years n=26 ≥ 75 years n=3	55 years (26 - 76)	54/46
Add-on Combination Therapy with Metformin and a Sulfonylurea				
Multicentre, randomized, double-blind, placebo-controlled	open-label metformin (≥ 1500 mg) and a sulfonlyurea (≥ 50% of the maximum dose) plus saxagliptin 5 mg or open-label metformin (≥ 1500 mg) and a sulfonlyurea (≥ 50% of the maximum dose) plus placebo Oral, 24 weeks	Saxagliptin 5 mg N=129 ≥ 65 years N=28 ≥ 75 years N=2 Placebo N=128 ≥ 65 years n=33 ≥ 75 years n=7	57 years (25 – 83)	60/40
Add-on Combination Therapy with Insulin (with or without Metformin)				

Trial design	Dosage, route of administration and duration	Study subjects per treatment arm Subjects ≥ 65 years of age Subjects ≥ 75 years of age (N=number)	Mean age (Range)	Gender (% M/F)
Multicentre, randomized, double-blind, placebo-controlled	open-label insulin (≥ 30 units/day, ≤ 150 units/day) alone or with metformin plus saxagliptin 5 mg or open label insulin (≥ 30 units/day, ≤ 150 units/day) alone or with metformin plus placebo Oral, 24 weeks	Saxagliptin 5 mg N=304 ≥ 65 years N=71 ≥ 75 years N=6 Placebo N=151 ≥ 65 years n=33 ≥ 75 years n=3	57 years (18 – 77)	41/59

Study results

Saxagliptin Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this randomized, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of saxagliptin in combination with metformin in patients with inadequate glycemic control (A1C ≥ 7% and ≤ 10%) on metformin alone. Patients were required to be on a stable dose of metformin (1500 mg to 2550 mg daily) for at least 8 weeks to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, two-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily for the duration of the study. Following the lead-in period, eligible patients were randomized 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 glycemic 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 A1C, FPG, and PPG compared with the placebo plus metformin group (Table 6).

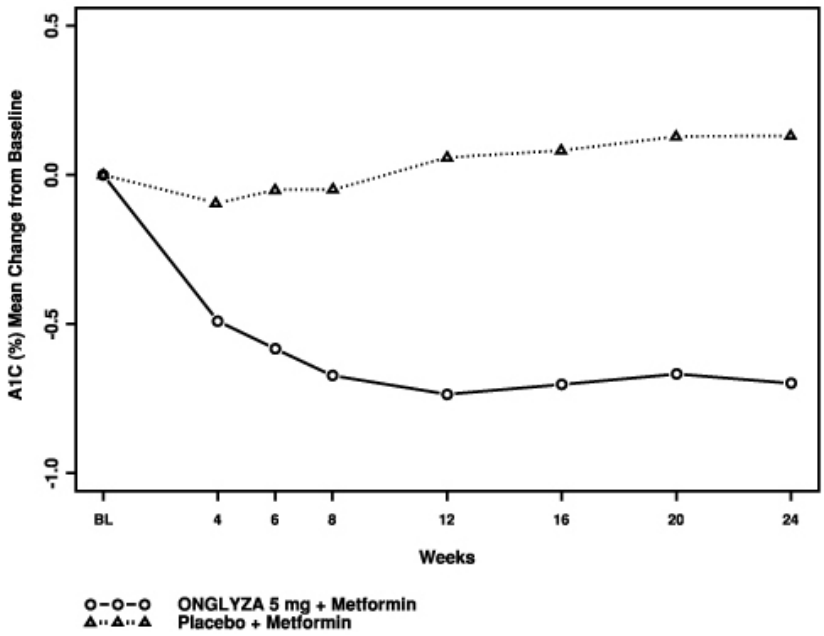
Table 6 Glycemic Parameters at Week 24 in a Placebo-Controlled Study of Saxagliptin in Combination with Metformin[§]

Efficacy Parameter	Saxagliptin 5 mg + Metformin	Placebo + Metformin
A1C (%)	**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[a]	
95% Confidence Interval	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	44%[a] (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	0.07
Difference from placebo (adjusted mean[±])	-1.3[a]	
95% Confidence Interval	(-1.7, -0.9)	
2-hour PPG (mmol/L)	**N=155**	**N= 135**
Baseline (mean)	16.4	16.4
Change from baseline (adjusted mean[±])	-3.2	-1.0
Difference from placebo (adjusted mean[±])	-2.2[a]	
95% Confidence Interval	(-3.1, -1.3)	
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 [a]	
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.
a p-value <0.0001 compared to placebo

The mean percent change from baseline in A1C over the 24-week period is shown in Figure 1. The proportion of patients achieving A1C <7% (regardless of baseline value) was significantly greater in the saxagliptin 5 mg plus metformin treatment (43.5%) groups compared with the placebo plus metformin group (16.6%). 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 –1.0 mmol/L in the placebo plus metformin group. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was higher in the placebo plus metformin group (27%) than in the saxagliptin 5 mg plus metformin group (13%). Higher baseline A1C was associated with a greater adjusted mean change from baseline in A1C with saxagliptin 5 mg. The effect of saxagliptin on lipid endpoints in this study was similar to placebo. Similar changes in body weight were observed in patients who received saxagliptin and placebo therapy (-0.9 kg and -0.9 kg, respectively).

Figure 1 **Mean Change from Baseline in A1C 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 Study Extension

Patients who completed all visits during the initial 24-week study period without need for hyperglycemia rescue therapy were eligible to enter a controlled double blind long-term study extension. Of the patients that started the 24-week treatment, 162 (84.8%) and 149 (83.2%) patients were taking saxagliptin 5 mg plus metformin and placebo plus metformin respectively. Patients who received saxagliptin in the initial 24-week study period maintained the same dose of saxagliptin in the long-term extension. Treatment with saxagliptin 5 mg plus metformin was associated with a greater reduction in A1C than in the placebo plus metformin group, and the effect relative to placebo was sustained at Week 50 and Week 102 compared to placebo. The A1C change for saxagliptin 5 mg plus metformin (n=100 observed, n=187 LOCF [last observation carried forward]) compared with placebo plus metformin (n=59 observed, n=175 LOCF) was -0.7% at Week 50. The A1C change for saxagliptin 5 mg plus metformin (n=31 observed, n=184 LOCF) compared with placebo plus metformin (n=15 observed, n=172 LOCF) was -0.7% at Week 102.

Saxagliptin Add-On Combination Therapy with Metformin and a Sulfonylurea

A total of 257 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin in combination with metformin and a sulfonylurea in patients with inadequate glycemic control (A1C ≥ 7% and ≤ 10%) on a stable combined dose of metformin (≥ 1500 mg) and sulfonylurea (≥ 50% of the maximum recommended dose) for at least eight weeks prior to enrollment.

Patients who met eligibility criteria were entered in a 2-week enrollment period to allow assessment of inclusion/exclusion criteria. Following the 2-week enrollment period, eligible patients were randomized 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, patients continued metformin and sulfonylurea at the same constant dose ascertained during enrollment. Sulfonylurea could be down titrated once in the case of a major hypoglycemic event or recurring minor hypoglycemic events. In the absence of hypoglycemia, titration (up or down) of study medication during the treatment period was prohibited.

Saxagliptin, in combination with metformin and a sulfonylurea, provided significant improvements in A1C and PPG compared with placebo in combination with metformin and a sulfonylurea (Table 7).

Table 7 Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Metformin and a Sulfonylurea*

Efficacy Parameter	**Saxagliptin 5 mg + Metformin and a Sulfonylurea N=129**	**Placebo + Metformin and a Sulfonylurea N=128**
A1C (%)	**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 A1C <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¶	
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 and a sulfonylurea
§ Significance not tested.
¶ p-value = 0.0301 compared to placebo + metformin and a sulfonylurea
# Not statistically significant.

Saxagliptin Add-On Combination Therapy with Insulin (with or without Metformin)

A total of 455 patients with type 2 diabetes participated in this randomized, double-blind, placebo-controlled trial of 24-week duration to evaluate the efficacy and safety of saxagliptin in combination with insulin in patients with inadequate glycemic control (A1C ≥7.5% and ≤11%) on insulin alone (N=141) or on 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 were on intermediate- or long-acting (basal) insulin or premixed insulin. 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 randomized 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 glycemic goals or who increased their insulin dose by >20% were rescued and subsequently switched to a flexible insulin dose regimen. 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 A1C and PPG compared with placebo add-on to insulin with or without metformin (Table 8). Similar A1C 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 glycemic 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. The mean daily insulin dose at baseline was 53 units in patients treated with saxagliptin 5 mg and 55 units in patients treated with placebo. The mean change from baseline in daily dose of insulin was an increase of 2 units for the saxagliptin 5 mg group and 5 units for the placebo group.

Table 8 Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Insulin*

Efficacy Parameter	Saxagliptin 5 mg + Insulin (+/− Metformin) N=304	Placebo + Insulin (+/− Metformin) N=151
Hemoglobin A1C (%)	**N=300**	**N=149**
Baseline (mean)	8.7	8.7
Change from baseline (adjusted mean†)	−0.7	−0.3
Difference from placebo (adjusted mean†)	−0.4‡	
95% Confidence Interval	(−0.6, −0.2)	
Percent of patients achieving A1C <7%	17%§ (52/300)	7% (10/149)
2-hour Postprandial Glucose (mmol/L)	**N=262**	**N=129**
Baseline (mean)	13.9	14.2
Change from baseline (adjusted mean†)	−1.5	−0.2
Difference from placebo (adjusted mean†)	−1.3¶	
95% Confidence Interval	(−2.1, −0.5)	
Fasting Plasma Glucose (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 + insulin
§ Significance not tested
¶ p-value = 0.0016 compared to placebo + insulin
\# Not statistically significant

Controlled Long-Term Study Extension

Following completion of the 24-week short-term treatment period, patients were eligible to enter a controlled double blind long-term treatment period. Patients continued to take the same blinded study medication that they were assigned during the short-term treatment period (saxagliptin 5 mg or placebo added on to insulin with or without metformin). During the long-term treatment extension, changes in both the dose and type of insulin were allowed. Of the patients that continued into the long-term treatment period, 268 (88.2% of randomized) patients and 134 (88.7% of randomized) patients were taking saxagliptin 5 mg and placebo plus insulin with or without metformin, respectively. Results from the extension period demonstrated that reductions from baseline A1C seen in the saxagliptin 5 mg add-on to insulin group compared with the placebo add-on to insulin group were sustained to Week 52; the A1C change for saxagliptin 5 mg (n=244 observed) compared with placebo (n=124 observed) was -0.4% at Week 52. Results were similar for subjects using metformin and not using metformin at baseline. Increases from baseline in mean total daily dose of insulin (MTDDI) were seen in both treatment groups through Week 52, with a numerically smaller increase in the saxagliptin 5 mg group (5 units saxagliptin versus 6 units Placebo).

Metformin

The prospective randomized (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

-a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034

-a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017

-a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)

-a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

DETAILED PHARMACOLOGY

Saxagliptin

Saxagliptin and its major metabolite are potent reversible inhibitors of DPP-4 *in vitro* with selectivity for DPP-4 versus other enzymes, including other DPP family members such as DPP-8 and DPP-9. Saxagliptin and its major metabolite have extended binding to the DPP-4 active site, prolonging their activity, but do not have extended duration of binding to other

enzymes, including DPP-8 and DPP-9. Saxagliptin was a potent inhibitor of T-cell cell surface DPP activity in cell based assays, but did not inhibit T-cell activation either *in vitro* or *in vivo*.

Saxagliptin, when dosed orally, demonstrated dose-related inhibition of DPP-4 in *ex vivo* assays in rats, dogs and cynomolgus monkeys. In acute *in vivo* studies, saxagliptin increased concentrations of intact GLP-1 in response to a meal in lean rats (maximum effect at 1 mg/kg). Saxagliptin also increased plasma insulin and lowered plasma glucose following an oral glucose tolerance test in obese insulin resistant and diabetic animal rodent models (maximum effect range 0.4 to 1.3 mg/kg). In chronic dosing studies using the progressively diabetic ZDF rat model, saxagliptin (4 mg/kg/day) delayed development of fasting hyperglycemia and the results of oral glucose tolerance tests showed significantly improved glucose homeostasis. These results are consistent with the mechanism of action of saxagliptin and its effects as an anti-hyperglycemic agent.

Metformin hydrochloride

Animal studies with metformin, labelled with ^{14}C have shown that the drug is neither concentrated by liver cells nor is it excreted in the bile; it is concentrated in the intestinal mucosa and salivary glands.

It has been shown that, following a 2 g dose of metformin, the blood level remains under 10 mcg/mL even at the peak, occurring 2 hours after absorption. During the experiments, metformin was shown to be devoid of any notable action in the body, apart from its specific metabolic activity.

In the healthy animal, metformin lowers blood sugar only at a nearly lethal dose. Different animal species are of unequal sensitivity. On the other hand, the animal with experimental diabetes, is sensitive to a much lower dosage, providing some insulin is still secreted.

The antihyperglycemic action of metformin is probably mediated through insulin by improving the glucose assimulation coefficient (K), and the insulin efficiency coefficient.

In the obese diabetic with hyperinsulinemia, metformin is reported to normalize insulin output. This normalizing effect is concurrent to that of glycemia.

Metformin has little effect on liver glycogen of the healthy animal. In low and average doses, no change occurs. In high doses nearing lethal levels, liver glycogen decreases. This lowering precedes the fall in blood sugar. This reaction represents a defense mechanism tending to mobilize body reserves in order to combat hypoglycemia.

In the diabetic animal with a low liver glycogen reserve, the opposite occurs and metformin builds up glycogen stores of the liver. *In vitro*, on muscular tissue isolated in Warburg's apparatus, metformin increases glucose uptake by the muscle. This action follows an aerobic pathway. Even in high concentration, contrary to phenethyl-biguanide, metformin apparently does not block respiration or change carbohydrate metabolism via the anaerobic pathway.

Metformin is eliminated in faeces and urine. It is rapidly excreted by the kidneys in an unchanged form.

Renal clearance is 450 mL/minute; this appears to explain the absence of accumulation.

Metabolites of metformin have not been identified, neither by radio-active nor by chemical methods.

A single Rf spot is always present following radiochromatographic study of urine and always corresponds to that of pure metformin. Administration during 10 consecutive days has not shown any sign of accumulation.

Inhibition of glyconeogenesis has been observed in animals following its stimulation by fasting, cortisol, alcohol or other substrates such as alanine lactate or pyruvate. However, such an effect varies according to the type and dosage of the biguanide used, nutritional state of the animal species and design of experimental model.

This inhibition of glyconeogenesis is observed only in the presence of insulin and it does not appear to play an important role in man.

Inhibition of intestinal absorption of sugars, which is not related to a malasorption phenomenon has been observed with biguanides under certain experimental conditions in animal and in man. In one study, a 20% retardation of galactose absorption was observed in man receiving metformin. However, such an effect of metformin could not be confirmed in another study in man.

Recent findings appear to indicate that most of the metabolic effects of the biguanides are exerted through a single mechanism, namely inhibition of fatty acid oxidation and of acetyl-CoA generation.

However, inhibition of insulin-stimulated lipogenesis which has also been observed appears to be due to the inhibition of acetyl-CoA carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect exerted by these drugs in obese diabetic patients.

TOXICOLOGY

No animal studies have been conducted with the combined products in KOMBOGLYZE (saxagliptin/metformin hydrochloride) to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based on the findings in studies with saxagliptin and metformin individually.

Acute Toxicity

Saxagliptin

Saxagliptin was observed to be well tolerated at single doses up to 2000 mg/kg in mice and rats and 25 mg/kg in cynomolgus monkeys. In rodents, 4000 mg/kg resulted in transient decreases in body-weight gain and activity and/or lethality. In monkeys, overt toxicity and lethality were observed at 50 mg/kg.

Chronic Toxicity

Saxagliptin and metformin hydrochloride

The repeat-dose toxicity of saxagliptin and metformin was evaluated in a 3-month dog study at doses of 5 mg/kg/day saxagliptin, 20 mg/kg/day metformin, and the combination of 1/20

and 5/20 mg/kg/day saxagliptin/metformin. Coadministration of saxagliptin and metformin did not induce unique or additive toxicities in dogs. The no-observed-adverse effect-level (5/20 mg/kg of saxagliptin/metformin) was 68 times and 1.5 times the human exposure based on the maximum recommended human doses of 5 mg/day of saxagliptin and 2000 mg/day of metformin, respectively.

Saxagliptin

The potential toxicity of saxagliptin was evaluated in a number of repeat-dose studies in mice, rats, dogs and monkeys. Saxagliptin administered to rats for 6 months at doses of 2, 20 and 100 mg/kg/day was well tolerated, causing only at the high dose, minimal splenic lymphoid hyperplasia and pulmonary histiocytosis. The no-observed-adverse-effect-level (20 mg/kg/day) was 36 times (males) and 78 times (females) the human exposure based on the recommended human dose of 5 mg/day (RHD). In dogs, saxagliptin administered orally at 5 and 10 mg/kg/day for 12 months caused toxicity in the intestinal tract, as evidenced by bloody and mucoid feces. The no-observed-adverse-effect-level was 1 mg/kg/day, 4 times the RHD. In monkeys, major target organ changes included skin lesions (scabs, erosions, and ulceration), lymphoid hyperplasia (primarily spleen and bone marrow) and multi-tissue mononuclear-cell infiltrates. Skin healing during the dosing period was observed with recovery of both skin and microscopic changes following a drug-free recovery period. The AUCs at the no effect level for these changes were 1 to 3 times the RHD.

Carcinogenicity

Saxagliptin

Two-year carcinogenicity studies were conducted in mice and rats at oral doses of 50, 250, and 600 mg/kg/day and 25, 75, 150, and 300 mg/kg/day, respectively. Saxagliptin did not induce tumors in either mice or rats at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 900 (males) and 1210 (females) times the human exposure at the recommended human dose of 5 mg/day (RHD). In rats, AUC exposures were approximately 370 (males) and 2300 (females) times the RHD.

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.

Mutagenesis

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.

Reproduction

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 630 (males) and 805 (females) times human exposure at the RHD. At higher, maternally toxic doses (300 and 750 mg/kg/day), increased fetal resorptions were observed (approximately 2150 and 6375 times the RHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at 750 mg/kg (approximately 6375 times the RHD).

Metformin hydrochloride

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

Development

Saxagliptin and metformin hydrochloride

Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species at doses up to 25/600 mg/kg/day in rats (AUC exposures 100 and 10 times the maximum recommended human dose (MRHD) of 5 mg saxagliptin and 2000 mg metformin, respectively) and 40/50 mg/kg/day in rabbits (AUC exposures 249 and 1.1 times the MRHD of saxagliptin and metformin, respectively).

In rats, an increased incidence of delayed rib ossification (a minor developmental toxicity) was observed in fetuses of females dosed at 25/600 mg/kg/day of saxagliptin/metformin. This finding occurred in the presence of maternal toxicity which included 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 of saxagliptin/metformin at 40/50 mg/kg/day was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. The increased mortality in gravid rabbits was metformin-related and species-specific (not seen in rats). Among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29. Associated developmental toxicity was observed in these litters which included fetal body weight decrements of 7%, 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 and reversible developmental delay in ossification of the fetal pelvis at ≥ 240 mg/kg/day (≥ 1560 times the human exposure [AUC] at the RHD). Maternal toxicity and reduced fetal body weights were observed at 900 mg/kg/day (8290 times the RHD). In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (200 mg/kg/day, exposures 1420 times the RHD).

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 ≥ 1690 times the RHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 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.

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PART III:
CONSUMER INFORMATION

PrKOMBOGLYZE®

saxagliptin and metformin hydrochloride tablets (as saxagliptin hydrochloride and metformin hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when KOMBOGLYZE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about KOMBOGLYZE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

WHAT THE MEDICATION IS USED FOR:
KOMBOGLYZE is used in addition to diet and exercise to improve blood sugar levels in adult patients with type 2 diabetes, who are already treated with:

- saxagliptin (ONGLYZA®) and metformin or who are not controlled on metformin alone.
- saxagliptin (ONGLYZA®), metformin and sulfonylurea or who are not controlled on metformin and sulfonylurea alone.
- saxagliptin (ONGLYZA®), metformin and insulin or who are not controlled on metformin and insulin alone.

WHAT IT DOES:
KOMBOGLYZE contains saxagliptin and metformin hydrochloride.

Saxagliptin belongs to a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors). Saxagliptin helps to improve blood sugar levels in response to a meal. Saxagliptin also lowers blood sugar levels between meals, and helps to decrease the amount of sugar made by your body.

Metformin is a member of the biguanide class of medicines, it helps to lower the amount of sugar made by the liver.

What is Type 2 Diabetes?
Insulin is a hormone that helps control the level of sugar (glucose) in your blood. Type 2 diabetes is a condition in which your body does not make enough insulin and/or the insulin that your body produces does not work as well as it should. When this happens, glucose can build up in the blood. This can lead to serious problems.

WHEN IT SHOULD NOT BE USED:
Do not take KOMBOGLYZE if you:

- Have unstable and/or insulin-dependent (Type 1) diabetes mellitus.
- Have metabolic acidosis [including diabetic ketoacidosis (increased ketones in the blood or urine) or lactic acidosis (too much acid in the blood), or history of ketoacidosis or lactic acidosis)]
- Have or have had a liver or kidney problem
- Have heart failure or cardiovascular collapse (abrupt failure of blood circulation) or cardiorespiratory insufficiency
- Drink a lot of alcohol
- Are stressed, have severe infections, are experiencing trauma, prior to surgery or during the recovery phase
- Suffer from severe dehydration (have lost a lot of water from your body)
- Are breastfeeding
- Are pregnant or planning to become pregnant
- Are going to get or receive an injection of dye or contrast agent for an x-ray procedure. Talk to your physician or pharmacist about when to stop KOMBOGLYZE and when to start again
- Are allergic (including angioedema / anaphylaxis) to saxagliptin, metformin or any of the ingredients in KOMBOGLYZE (see "WHAT THE NONMEDICINAL INGREDIENTS ARE") or if you are allergic to other drugs belonging to the DPP-4 class.

WHAT THE MEDICINAL INGREDIENT IS:
Saxagliptin (as saxagliptin hydrochloride) and metformin hydrochloride.

WHAT THE NONMEDICINAL INGREDIENTS ARE:
Magnesium stearate, polyvinyl alcohol, polyethylene glycol 3350, povidone, titanium dioxide, talc, and red iron oxide (2.5mg/500mg strength) or yellow iron oxide (2.5mg/1000mg strength) or a combination of red and yellow iron oxides (2.5mg/850mg strength).

WHAT DOSAGE FORMS IT COMES IN:
KOMBOGLYZE is supplied as tablets containing saxagliptin / metformin hydrochloride 2.5mg/500mg, 2.5mg/850mg or 2.5mg/1000mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

KOMBOGLYZE contains metformin and it can rarely cause lactic acidosis. Lactic acidosis can cause death and must be treated in the hospital. Alcohol may increase the risk of lactic acidosis. Do not drink a lot of alcohol while taking KOMBOGLYZE.

Lactic Acidosis

Stop taking KOMBOGLYZE and tell your doctor if you get the following symptoms of lactic acidosis:

- You feel very weak and tired

- You have unusual (not normal) muscle pain
- You have trouble breathing
- You have stomach pain with nausea and vomiting, or diarrhea
- You feel cold, especially in your arms and legs
- You feel dizzy or lightheaded
- You feel unusual fatigue and drowsiness
- You have a slow or irregular heart beat
- Your medical condition suddenly changes

BEFORE you use KOMBOGLYZE talk to your doctor or pharmacist if:

- You have or have had any kidney problems
- You have or have had liver problems
- You have or have had heart failure
- You consume large quantities of alcohol all the time or short term "binge"
- You are dehydrated (have lost a large amount of body fluids. This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and don't drink enough fluids.)
- You will have certain x-ray tests with injectable dyes or contrast agents
- You will be having surgery
- You have had a heart attack, severe infection, or stroke
- You feel very weak and tired
- You have had an allergic reaction to other DPP-4 inhibitors
- You have or have had diabetic ketoacidosis (increased ketones in the blood or urine)
- You are pregnant or planning to become pregnant
- You are breast-feeding or plan to breast-feed
- You are 80 years of age or older and have not had your kidney function tested
- You have or have had pancreas problems such as inflammation of the pancreas (pancreatitis)
- You have low B_{12} levels

Heart Failure has been seen in patients treated with KOMBOGLYZE. **Heart Failure** is when your heart is unable to pump enough blood to meet the needs of the body. You are at greater risk of **Heart Failure** if you have or have had:

- heart or blood vessel disease including heart failure and heart attack
- kidney disease
- several risk factors of getting heart disease

Symptoms of heart failure include one or more of the following: tiredness, swollen ankles, a fast increase in weight and increased shortness of breath especially when lying down. This is serious. You must talk to your physician immediately or go to the hospital if this happens to you.

KOMBOGLYZE is not recommended for use in children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Some drugs may interact with KOMBOGLYZE. Tell your doctor if you are taking:

- Other diabetes drugs such as glyburide
- Furosemide
- Nifedipine
- Cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin)
- Other drugs tend to produce hyperglycemia (high blood sugar) and may lead to a loss of blood sugar control. Some example of drugs that can increase the blood sugar include:
  - Thiazide and other diuretics (water pills)
  - Corticosteroids
  - Phenothiazines
  - Thyroid products
  - Estrogens or estrogens plus progestogen
  - Oral contraceptives
  - Phenytoin
  - Nicotinic Acid
  - Sympathomimetics
  - Calcium channel blocking drugs
  - Isoniazid
  - Beta-2-agonists
- ACE inhibitor drugs (may lower blood glucose)

Talk to your doctor or pharmacist about all the drugs you take. This includes prescription drugs, as well as those you buy yourself, and herbal supplements.

PROPER USE OF THIS MEDICATION

Follow the directions given to you by your doctor. Your doctor will tell you how many KOMBOGLYZE tablets to take and how often you need to take them.

KOMBOGLYZE is to be taken twice a day with meals.

OVERDOSE:

If you use more KOMBOGLYZE tablets than you should or in case of a suspected drug overdose, contact your doctor, or nurse, or regional Poison Control Centre immediately, even if there are no symptoms.

MISSED DOSE:

If you miss a dose of KOMBOGLYZE, take it with food as soon as you remember. If you do not remember until it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects: upper respiratory tract infection, urinary tract infection, headache, diarrhea, nausea, upset stomach, abdominal bloating, gas, and loss of appetite.

Hypoglycemia may occur more frequently in people who already take a sulfonylurea or insulin. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include shaking, sweating, rapid heartbeat, change in vision, hunger, headache, and change in mood.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon			
Pancreatitis (inflammation of the pancreas): prolonged severe abdominal pain which may be accompanied by vomiting.		X	X
Severe disabling joint pain.		X	
Rare			
Lactic Acidosis (build up of lactic acid in your blood): • feeling very weak, tired or uncomfortable • unusual muscle pain • trouble breathing • unusual or unexpected stomach discomfort • feeling cold • feeling dizzy or lightheaded • unusual fatigue and drowsiness • suddenly develop a slow or irregular heartbeat.			X
Very rare			
Allergic (hypersensitivity) reactions (angioedema / anaphylaxis): swelling of the face, lips or throat, difficulty breathing, rash, hives, itching, peeling, or flaking skin.		X	X
Bullous pemphigoid (serious skin reaction): blistering of the skin, redness, peeling skin.		X	
Unknown			
Heart failure (a weakness of the heart): tiredness, swollen ankles, increasing shortness of breath especially when lying down and a fast increase in weight.			X

This is not a complete list of side effects. For any unexpected effects while taking KOMBOGLYZE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15-25°C).

Keep KOMBOGLYZE well out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing.

The most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at:
www.astrazeneca.ca or by contacting the sponsor, AstraZeneca Canada Inc. at:
Customer Inquiries 1-800-668-6000,
Renseignements 1-800-461-3787.

This leaflet was prepared by:
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