נובמבר 2019

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

KOMBIGLYZE XR tablets 2.5mg/1000mg: פרסום עדכון בעלון התכשיר
KOMBIGLYZE XR tablets 5mg/1000mg

הרכב:
KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets 2.5mg/1000mg
KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets 5mg/1000mg
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התוויה:
KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **אוגוסט 2019.**

העדכון העיקרי בעלון לרופא הוא:

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. ~~Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.~~The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, ~~increasing~~ somnolence, and ~~nonspecific~~ abdominal pain ~~distress~~. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (> 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [see *Warnings and Precautions (5.1)*]. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g.,carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.**
- **Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the full prescribing information [see *Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue KOMBIGLYZE XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see *Warnings and Precautions (5.1)*].**

2.3 Recommendations for Dosing and Administration in patients with Renal Impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed

more frequently, e.g. every 3-6 months. Factors that may increase the risk of lactic acidosis (see *Warnings and Precautions (5.1) should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.*
If no adequate strength of Kombiglyze XR is available, individual monocomponents should be used instead of the fixed dose combination

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

1. Contraindications

Severe renal impairment (eGFR below 30 mL/min/1.73 m2).~~Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia~~

5. WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis.~~Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with KOMBIGLYZE XR; 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.~~

Metformin-associated Lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/L), ~~decreased blood pH, electrolyte disturbances with an~~ increased anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.~~When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found~~.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of KOMBIGLYZE XR.

In KOMBIGLYZE XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue KOMBIGLYZE XR and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The post-marketing metformin-associated lactic acidosis cases primarily occurred in
patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include [see Clinical Pharmacology (12.3)].

- Before initiating KOMBIGLYZE XR, obtain an estimated glomerular filtration rate (eGFR).
- KOMBIGLYZE XR is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m2 [see Contraindications (4)].
- Initiation of KOMBIGLYZE XR is not recommended in patients with eGFR between 30 and 45 mL/minute/1.73 m2
- Obtain an eGFR at least annually in all patients taking KOMBIGLYZE XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking KOMBIGLYZE XR whose eGFR later falls below 45 mL/minute/1.73 m2 assess the benefit and risk of continuing therapy.

Drug Interactions: The concomitant use of KOMBIGLYZE XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation [see Drug Interactions (7)]. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see Use in Specific Populations (8.5)].

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop KOMBIGLYZE XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart KOMBIGLYZE XR if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may
increase the risk for volume depletion, hypotension and renal impairment. KOMBIGLYZE XR should be
temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the post-marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and
hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions
associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue KOMBIGLYZE XR.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving KOMBIGLYZE XR.

Hepatic Impairment: Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of KOMBIGLYZE XR in patients with clinical or laboratory evidence of hepatic disease.

~~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 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 *Warnings and Precautions (5.3, 5.6, 5.7, 5.11)*].~~

~~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 [see *Warnings and Precautions (5.12)*]. 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. [See *Warnings and Precautions (5.8)*.] 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 (4)* and *Warnings and Precautions (5.6, 5.7, 5.10, 5.11, 5.12)*].~~

a. Pancreatitis

There have been post-marketing reports of acute pancreatitis in patients taking saxagliptin. In a cardiovascular outcomes trial enrolling participant with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), cases of definite acute pancreatitis were confirmed in 17 of 8240 (0.2%) patients receiving saxagliptin compared to 9 of 8173 (0.1%) receiving placebo. Pre-existing risk factors for pancreatitis were identified in 88% (15/17) of those patients receiving saxagliptin and in 100% (9/9) of those patients receiving placebo.

After initiation of KOMBIGLYZE XR, observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue KOMBIGLYZE and initiate 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 KOMBIGLYZE XR.

~~In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the incidence of adjudicated pancreatitis events was 0.3% in both saxagliptin-treated patients and placebo-treated patients in the intent-to-treat population. (See 6.1 **Clinical trials experience)**.~~

~~5.3 Assessment of Renal Function~~

~~Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, KOMBIGLYZE XR is contraindicated in patients with renal impairment [see *Contraindications (4)*].~~

~~Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and KOMBIGLYZE XR discontinued if evidence of renal impairment is present.~~

b. Heart Failure

In a cardiovascular outcomes trial enrolling participant with established ASCVD or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to saxagliptin (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of hospitalization for heart failure was higher in the saxagliptin group (estimated Hazard Ratio: 1.27; 95% CI: 1.07, 1.51).

Subjects with a prior history of heart failure and subjects with renal impairment had a higher risk for hospitalization for heart failure, irrespective of treatment assignment.

Consider the risks and benefits of KOMBIGLYZE XR prior to initiating treatment in patients at a higher risk for heart failure. Observe patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure, and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of KOMBIGLYZE XR.

~~5.4 Impaired Hepatic Function~~

~~Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, KOMBIGLYZE XR is not recommended in patients with hepatic impairment.~~

~~5.6 Alcohol Intake~~

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

~~5.7 Surgical Procedures~~

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

~~5.8 Cardiac Failure~~

~~In the SAVOR trial an increase in the rate of hospitalization for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established. Caution is warranted if TRADENAME is used in patients who have known risk factors for hospitilisation for heart failure, such as a history of heart failure or moderate to severe renal impairment.30 Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms. (see 14.6 Cardiovascular safety)~~

~~5.11 Concomitant Medications Affecting 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 (7.2)*], should be used with caution.~~

~~5.12 Radiologic Studies with Intravascular Iodinated 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. Therefore, in patients in whom any such study is planned, KOMBIGLYZE XR~~

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.

5.13 Hypoxic States

Cardiovascular collapse (shock), 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 KOMBIGLYZE XR therapy, the drug should be promptly discontinued.

5.8 Severe and Disabling Arthralgia

There have been post-marketing reports of severe and disabling arthralgia in patients taking DPP4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP4 inhibitor. Consider DPP4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.9 Bullous Pemphigoid

Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving KOMBIGLYZE XR. If bullous pemphigoid is suspected, KOMBIGLYZE XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In randomized, controlled, double-blind clinical trials, over 17.000 patients with type 2 diabetes have been treated with saxagliptin

6.1.1. Adverse reactions associated with saxagliptin in the SAVOR trial

The SAVOR trial included 8240 patients treated with saxagliptin 5 mg or 2.5 mg once daily and 8173 patients on placebo. The mean duration of saxagliptin exposure regardless of interruptions was 1.8 years. A total of 3698 patients (45%) were treated with saxagliptin for between 2 and 3 years.

The overall incidence of adverse events in patients treated with saxagliptin in this trial was similar to placebo (72.5% versus 72.2%, respectively). Discontinuation of therapy due to adverse events was similar between the two treatment groups (4.9% in the saxagliptin group and 5.0% in the placebo group).

The cardiovascular safety of saxagliptin was evaluated in the SAVOR trial which established that saxagliptin did not increase the cardiovascular risk (CV death, nonfatal MI, or nonfatal ischemic stroke) in patients with type 2 diabetes mellitus (T2DM) compared to placebo when added to current background therapy (Hazard Ratio [HR] 1.00; 95% Confidence Interval [CI]: 0.89, 1.12; P<0.001 for noninferiority). (See **14.6 Cardiovascular Safety**).

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

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

~~***Hypoglycemia***~~

~~In the SAVOR trial, the overall incidence of reported hypoglycemia (recorded in daily patient diaries) was 17.1% in saxagliptin-treated patients and 14.8% in placebo-treated patients The percent of subjects with reported on-treatment events of major hypoglycemia (defined as an event that required assistance of another person) was higher in the saxagliptin group than in the placebo group (2.1% and 1.6%, respectively). The increased risk of overall hypoglycemia and major hypoglycemia observed in the saxagliptin-treated group occurred primarily in subjects treated with a sulfonylurea at baseline and not in subjects on insulin or metformin monotherapy at baseline. The increased risk of overall and major hypoglycemia was primarily observed in subjects with A1C <7% at baseline~~

Adverse Reactions in Efficacy Trials

Metformin hydrochloride

In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with metformin extended-release.

Saxagliptin

~~In two placebo-controlled monotherapy trials of 24-week duration, patients were treated with saxagliptin 2.5 mg daily, saxagliptin 5 mg daily, and placebo. Three 24-week, placebocontrolled, add-on combination therapy trials were also conducted: one with metformin immediate-release, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with saxagliptin 2.5 mg daily, saxagliptin 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin immediate-release. The 10 mg saxagliptin dosage is not an approved dosage.~~

~~In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin immediate-release trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with saxagliptin 2.5 mg and saxagliptin 5 mg was similar to placebo (72% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively. The most common adverse events (reported in at least 2 patients treated with saxagliptin 2.5 mg or at least 2 patients treated with saxagliptin 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in 5% of patients treated with saxagliptin 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.~~

The data in Table 1 are derived from a pool of 5 placebo-controlled clinical trials [see Clinical Studies (14)]. These data shown in the table reflect exposure of 882 patients to saxagliptin and a mean duration of exposure to saxagliptin of 21 weeks. The mean age of these patients was 55 years, 1.4% were 75 years or older and 48.4% were male. The population was 67.5% White, 4.6% Black or African American, 17.4% Asian, Other 10.5% and 9.8% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 5.2 years and a mean HbA1c of 8.2%. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60mL/min/1.73m2) in 91% of these patients.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of saxagliptin. These adverse reactions occurred more commonly on saxagliptin than on placebo and occurred in at least 5% of patients treated with saxagliptin.

Table 1: Adverse Reactions in Placebo-Controlled Trials* Reported in ≥ 5% of Patients Treated with Saxagliptin 5 mg and More Commonly than in Patients Treated with Placebo

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

In the add-on to TZD trial, the incidence of peripheral edema was higher for saxagliptin 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for

saxagliptin 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for saxagliptin 2.5 mg and saxagliptin 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to ~~glyburide In this pooled analysis, adverse reactions that were reported in ≥ 2% of patients treated with saxagliptin 2.5 mg or saxagliptin 5 mg and ≥ 1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).~~

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for saxagliptin (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The 10 mg saxagliptin dosage is not an approved dosage. The incidence rate of fracture events in patients who received saxagliptin did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

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.

Discontinuation of therapy due to adverse reactions occurred in 2.2%, 3.3%, and 1.8% of subjects receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively. The most common adverse reactions (reported in at least 2 subjects treated with saxagliptin 2.5 mg or at least 2 subjects treated with saxagliptin 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%).

Renal Impairment

In the SAVOR trial, adverse reactions related to renal impairment, including laboratory changes (i.e., doubling of serum creatinine compared with baseline and serum creatinine >6 mg/dL), were reported in 5.8% (483/8280) of saxagliptin-treated subjects and 5.1% (422/8212) of placebo-treated subjects. The most frequently reported adverse reactions included renal impairment (2.1% vs. 1.9%), acute renal failure (1.4% vs. 1.2%), and renal failure (0.8% vs. 0.9%), in the saxagliptin versus placebo groups, respectively. From baseline to the end of treatment, there was a mean decrease in eGFR of 2.5 mL/min/1.73m^2 for saxagliptin-treated patients and a mean decrease of 2.4 mL/min/1.73m^2 for placebo-treated patients. More subjects randomized to saxagliptin (421/5227, 8.1%) compared to subjects randomized to placebo (344/5073, 6.8%) had downward shifts in eGFR from >50 mL/min/1.73 m^2 (i.e., normal or mild renal impairment) to ≤50 mL/min/1.73 m^2 (i.e., moderate or severe renal impairment). The proportions of subjects with renal adverse reactions increased with worsening baseline renal function and increased age, regardless of treatment assignment

Absolute Lymphocyte Counts

In the SAVOR trial mean decreases of approximately 84 cells/microL with saxagliptin relative to placebo was observed. The proportion of patients who experienced a

decrease in lymphocyte counts to a count of ≤750 cells/microL was 1.6% (136/8280) and 1.0% (78/8212) on saxagliptin and placebo respectively.

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

7 DRUG INTERACTIONS

7.1 Strong Inhibitors of CYP3A4/5 Enzymes

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of saxagliptin should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*.]

7.2 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with KOMBIGLYZE XR may increase the risk for lactic acidosis.

7.3 Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)]. Consider the benefits and risks of concomitant use.

7.4 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving KOMBIGLYZE XR.

7.5 Insulin Secretagogues or Insulin

In the saxagliptin add-on to sulfonylurea, add-on to insulin, and add-on to metformin plus sulfonylurea trials, confirmed hypoglycemia was reported more commonly in patients treated with saxagliptin compared to placebo. When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia.

~~7.2 Cationic Drugs~~

~~*Metformin hydrochloride*~~

~~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 healthy volunteers. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of KOMBIGLYZE XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system~~.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with KOMBIGLYZE XR or saxagliptin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see Data].

No adverse developmental effects independent of maternal toxicity were observed when saxagliptin and metformin were administered separately or in combination to pregnant rats and rabbits during the period of organogenesis [see Data].

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

~~Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the maximum recommended human doses (MRHD; saxagliptin 5 mg and metformin 2000 mg), respectively, in rats; and 249 and 1.1 times the MRHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of wavy ribs; associated maternal toxicity was limited to weight decrements of 11% to 17% over the course of the study, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to 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 tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form~~

~~of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the MRHD of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD.~~

~~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 (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.~~

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

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with an HbA1c greater than 7 and has been reported to be as high as 20 to 25% in women with an HbA1c greater than 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Saxagliptin

In embryo-fetal development studies, saxagliptin was administered to pregnant rats and rabbits during the period of organogenesis, corresponding to the first trimester of human pregnancy. No adverse developmental effects were observed in either species at exposures 1503-and 152-times the 5 mg clinical dose in rats and rabbits, respectively, based on AUC. Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

In a prenatal and postnatal development study, no adverse developmental effects were observed in maternal rats administered saxagliptin from gestation day 6 through lactation day 21 at exposures up to 470-times the 5 mg clinical dose, based on AUC

Metformin hydrochloride

Metformin hydrochloride did not cause adverse developmental effect when administered to pregnant Sprague Dawley rats and rabbits at doses up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2 and 6 times a 2000 mg clinical does based on body surface area (mg/m^2) for rats and rabbits, respectively.

Saxagliptin and Metformin

Saxagliptin and metformin coadministered to pregnant rats and rabbits during the period of organogenesis did not result in adverse developmental effects considered clinically relevant in either species. Doses tested in rats provided exposure up to 100-and 10-times clinical exposure, and doses tested in rabbits provided exposure up to 249-and 1-times clinical exposure relative to the clinical dose of 5 mg saxagliptin and 2000 mg metformin. Minor skeletal abnormalities associated with maternal toxicity were observed in rats. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29, associated with fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid bone.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KOMBIGLYZE XR or saxagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk [see Data]. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Saxagliptin is present in the milk of lactating rats [see Data].

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KOMBIGLYZE XR and any potential adverse effects on the breastfed child from KOMBIGLYZE XR or from the underlying maternal condition.

Data

Human

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Animals

No studies is lactating animals have been conducted with the combined components of KOMBIGLYZE XR. In studies performed with the individual components, both saxagliptin and metformin are secreted in the milk of lactating rats. Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations.

~~8.3 Nursing Mothers~~

~~No studies in lactating animals have been conducted with the combined components of KOMBIGLYZE XR. In studies performed with the individual components, both saxagliptin~~

~~and metformin are secreted in the milk of lactating rats. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE XR is administered to a nursing woman.~~

8.5 Geriatric Use

KOMBIGLYZE XR

Elderly patients are more likely to have decreased renal function. Assess renal function more frequently in the elderly [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]. ~~Because metformin is contraindicated in patients with renal impairment, carefully monitor renal function in the elderly and use KOMBIGLYZE XR with caution as age increases. [See *Warnings and Precautions (5.1, 5.3)* and *Clinical Pharmacology (12.3).*]~~

Saxagliptin

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

In the seven~~,six~~, double-blind, controlled clinical safety and efficacy trials of saxagliptin, a total of 4751 ~~634 (42.0%)(15.3%)~~of the 1130~~14148 randomized~~ patients randomized to saxagliptin were 65 years and over, and 1210 (10.7%) patients were 75 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. ~~No overall differences in safety or effectiveness were observed between patients 65 years and over, 75 years and over, and the younger patients.~~

8.6 Renal Impairment

Saxagliptin

In a 12-week randomized placebo-controlled trial, saxagliptin 2.5 mg was administered to 85 subjects with moderate (n=48) or severe (n=18) renal impairment or end-stage renal disease (ESRD) (n=19) [see Clinical Studies (14)]. The incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between saxagliptin and placebo. The overall incidence of reported hypoglycemia was 20% among subjects treated with saxagliptin 2.5 mg and 22% among subjects treated with placebo. Four saxagliptin-treated subjects (4.7%) and three placebo-treated subjects (3.5%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying fingerstick glucose ≤50 mg/dL).

Metformin hydrochloride

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. KOMBIGLYZE XR is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2 [see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. KOMBIGLYZE XR is not recommended in patients with hepatic impairment [see Warnings and Precautions (5.1)].

12.3 Pharmacokinetics
Specific Populations

Renal Impairment

Saxagliptin
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. The 10 mg dosage is not an approved dosage. The degree of renal impairment did not affect C_{max} of saxagliptin or its metabolite. In subjects with moderate renal impairment with eGFR 30 to less than 45 mL/min/1.73 m^2, severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m^2) and ESRD patient on hemodialysis, the AUC values of saxagliptin or its active metabolite were >2 fold higher than AUC values in subjects with normal renal function.

Metformin hydrochloride

In patients with decreased renal function (~~based on measured creatinine clearance~~, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [*see Contraindications (4) and Warnings and Precautions (5.1)*]. ~~in proportion to the decrease in creatinine clearance. Use of metformin in patients with renal impairment increases the risk for lactic acidosis. Because KOMBIGLYZE XR contains metformin, KOMBIGLYZE XR is contraindicated in patients with renal impairment [see *Contraindications (4)* and *Warnings and Precautions (5.3)*].~~

Hepatic Impairment

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment. ~~Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Because KOMBIGLYZE XR contains metformin, KOMBIGLYZE XR is not recommended in patients with hepatic impairment [see *Warnings and Precautions (5.4)*].~~

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity was evaluated 12 2-year studies conducted in CD-1 mice and Sprague-Dawley rats
Saxagliptin did not increase the incidence of tumors in mice dosed orally at 50, 250, and 600 mg/kg) up to 870–times (males) and 1165–times (females) the 5 mg/day clinical dose, based on AUC. Saxagliptin did not increase the incidence of tumors in rats dosed orally at 25, 75, 150, and 300 mg/kg up to 355□times (males) and 2217–times (females) the 5

mg/day clinical dose, based on AUC ~~(25, 75, 150, and 300 mg/kg) at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 870 (males) and 1165 (females) times the human exposure at the MRHD of 5 mg/day. In rats, exposures were approximately 355 (males) and 2217 (females) times the MRHD.~~

Impairment of Fertility

Saxagliptin administered to rats had no effect on fertility or the ability to maintain a litter at exposures up to 603-times and 776-times the 5 mg clinical dose in males and females, based on AUC. ~~In a rat fertility study, males were treated with oral gavage doses for 2 weeks prior to mating, during mating, and up to scheduled termination (approximately 4 weeks total) and females were treated with oral gavage doses for 2 weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at exposures of approximately 603 (males) and 776 (females) times the MRHD. Higher doses that elicited maternal toxicity also increased fetal resorptions (approximately 2069 and 6138 times the MRHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at approximately 6138 times the MRHD.~~

14 CLINICAL STUDIES

Saxagliptin Add-on Combination Therapy with Metformin plus an SGLT2 Inhibitor

A total of 315 patients with type 2 diabetes participated in this 24-week randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin added to dapagliflozin (an SGLT2 inhibitor) and metformin in patients with a baseline of HbA1c ≥7% to ≤10.5%. The mean age of these subjects was 54.6 years, 1.6% were 75 years or older and 52.7% were female. The population was 87.9% White, 6.3% Black or African American, 4.1% Asian, and 1.6% Other race. At baseline the population had diabetes for an average of 7.7 years and a mean HbA1c of 7.9%. The mean eGFR at baseline was 93.4 mL/min/1.73 m^2. Patients were required to be on a stable dose of metformin (≥1500 mg per day) for at least 8 weeks prior to enrollment. Eligible subjects who completed the screening period entered the lead in treatment period, which included 16 weeks of open-label metformin and 10 mg dapagliflozin treatment. Following the lead-in period, eligible patients were randomized to saxagliptin 5 mg (N=153) or placebo (N =162) [i]

The group treated with add-on saxagliptin had statistically significant greater reductions in HbA1c from baseline versus the group treated with placebo (see Table 12). [ii]

Table 12: HbA1c Change from Baseline at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On to Dapagliflozin and Metformin [§]

	Saxagliptin 5 mg (N=153) [†]	**Placebo (N=162)** [†]
	In combination with Dapagliflozin and Metformin	
Hemoglobin A1C (%) *		
Baseline (mean)	8.0	7.9
Change from baseline (adjusted mean[‡]) 95% Confidence Interval	-0.5 (−0.6, −0.4)	−0.2 (−0.3, −0.1)
Difference from placebo (adjusted mean) 95% Confidence Interval	−0.4[¶] (−0.5, −0.2)	

* Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing week 24 data.

† Number of randomized and treated patients.

‡ Least squares mean adjusted for baseline value. §

There were 6.5% (n=10) of randomized subjects in the saxagliptin arm and 3.1% (n=5) in the placebo arm for whom change from baseline HbA1c data was missing at week 24. Of the subjects who discontinued study medication early, 9.1% (1 of 11) in the saxagliptin arm and 16.7% (1 of 6) in the placebo arm had HbA1c measured at week 24.

¶ p-value <0.0001

The known proportion of patients achieving HbA1c <7% at Week 24 was 35.3% in the saxagliptin treated group compared to 23.1% in the placebo treated group. [iii]

14.2 Cardiovascular safety trial

~~**Instructions for Local Regulatory Personnel:** Where acceptable, use the text and data from this entire section. If not possible to submit this entire section, please contact the global team for assistance to agree on abbreviated text options.~~

~~In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the effect of saxagliptin on the occurrence of major cardiovascular disease (CVD) events was assessed in 16,492 adult patients with type 2 diabetes who had either established CVD or multiple risk factors for vascular disease, including patients with moderate or severe renal impairment. Patients ≥40 years of age, diagnosed with type 2 diabetes and with A1C ≥6.5%, and with either established CVD or multiple CV risk factors were enrolled.~~

~~Patients were randomly assigned to placebo (n=8212) or saxagliptin (5 mg or 2.5 mg for patients with moderate or severe renal insufficiency) once daily (n=8280). Randomization to the saxagliptin and placebo groups was stratified by CV risk with 3533 patients (21.4%) with CV risk factors only and 12,959 patients (78.6%) with established CVD and by renal impairment including 13,916 subjects (84.4%) with normal renal function to mild impairment, 2240 subjects (13.6%) with moderate impairment, and 336 subjects (2.0%) with severe renal impairment. Patients with established CVD were defined by a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke. Patients with CV risk factors only had age as a CV risk factor (men ≥55 years and women ≥60 years) plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking.~~

~~The demographics and baseline characteristics of subjects were balanced between the saxagliptin and placebo groups. The study population was 67% male and 33% female with a mean age at randomization of 65 years. Of the 16,492 patients randomized, 8561 (52%) patients were 65 years and over and 2330 (14%) were 75 years and over.~~

~~All study subjects had a mean duration of T2DM of 12 years (median = 10.3) and a mean A1C level of 8.0% (median = 7.6%). Overall, 25% of subjects had baseline A1C levels <7%. Subjects were followed for a mean duration of 2 (median = 2.0) years.~~

~~Concomitant medication use was similar for the two treatment groups. Overall, the use of diabetes medications was consistent with local treatment practice and the saxagliptin clinical program (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of CVD medications was also consistent with local treatment practice (ACE inhibitors or ARBs 79%, statins 78%, aspirin 75%, beta blockers 62%, and nonaspirin antiplatelet medications 24%).~~

Approximately 6% of subjects were treated with diet and exercise only at baseline. Concomitant medications were managed throughout the trial to local guideline targets for glycemic control and CV risk reduction in order to minimize differences between the two treatment groups, particularly for glycemic control.[i]

The primary safety and efficacy endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following major adverse CV events (MACE): CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke.

The primary safety objective of this trial was to establish that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite endpoint of CV death, non-fatal MI or non-fatal ischemic stroke observed with saxagliptin to that observed in the placebo group was <1.3.

The primary efficacy objective was to determine, as a superiority assessment, whether treatment with saxagliptin, compared with placebo when added to current background therapy, resulted in a significant reduction in the primary MACE endpoint.

The first secondary efficacy endpoint was a composite endpoint consisting of the time-to-first occurrence of MACE plus hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary revascularization (MACE plus). The next secondary efficacy endpoint was to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in subjects with T2DM would result in a reduction of all-cause mortality.

The cardiovascular safety of saxagliptin was evaluated in the SAVOR trial which established that saxagliptin did not increase the CV risk (CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke) in patients with T2DM compared to placebo when added to current background therapy (HR 1.00; 95% CI: 0.89, 1.12; P<0.001 for noninferiority).

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

Instructions for Local Regulatory Personnel: The following data displays have been prioritized for use in proposed local labeling. Use of both is recommended. However, if local regulations or guidelines only allow one to be submitted to your health authority, use the first.

The cardiovascular risk of saxagliptin was evaluated in SAVOR, a multicenter, multinational, randomized, double-blind study comparing saxagliptin (N=8280) to placebo (N=8212), both administered in combination with standard of care, in adult patients with type 2 diabetes at high risk for atherosclerotic cardiovascular disease. Of the randomized study subjects, 97.5% completed the trial, and the median duration of follow-up was approximately 2 years. The trial was event-driven, and patients were followed until a sufficient number of events were accrued.

Subjects were at least 40 years of age, had A1C ≥ 6.5%, and multiple risk factors (21% of randomized subjects) for cardiovascular disease (age ≥55 years for men and ≥60 years for women plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking) or established (79% of the randomized subjects) cardiovascular disease defined as a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke. The majority of subjects were male (67%) and Caucasian (75%) with a mean age of 65 years. Approximately 16% of the population had moderate (estimated glomerular

filtration rate [eGFR] ≥30 to ≤50 mL/min) to severe (eGFR <30 mL/min) renal impairment, and 13% had a prior history of heart failure. Subjects had a median duration of type 2 diabetes mellitus of approximately 10 years, and a mean baseline A1C level of 8.0%. Approximately 5% of subjects were treated with diet and exercise only at baseline. Overall, the use of diabetes medications was balanced across treatment groups (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of cardiovascular disease medications was also balanced (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs] 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antiplatelet medications 24%).

The primary analysis in SAVOR was time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event in SAVOR was defined as a cardiovascular death, or a nonfatal myocardial infarction (MI) or a nonfatal ischemic stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE and was also powered for a superiority comparison if non-inferiority was demonstrated.

The results of SAVOR, including the contribution of each component to the primary composite endpoint are shown in Table 13. The incidence rate of MACE was similar in both treatment arms: 3.8 MACE per 100 patient-years on placebo vs. 3.8 MACE per 100 patient-years on saxagliptin. The estimated hazard ratio of MACE associated with saxagliptin relative to placebo was 1.00 with a 95.1% confidence interval of (0.89, 1.12). The upper bound of this confidence interval, 1.12, excluded a risk margin larger than 1.3.

~~**Table 8: Primary and Secondary Clinical Endpoints by Treatment Group in the SAVOR Study***‡~~

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

* Intent-to-treat population

† Hazard ratio adjusted for baseline renal function category and baseline CVD risk category.

‡ P-value <0.001 for noninferiority (based on HR <1.3) compared to placebo.

§ P-value = 0.99 for superiority (based on HR <1.0) compared to placebo.

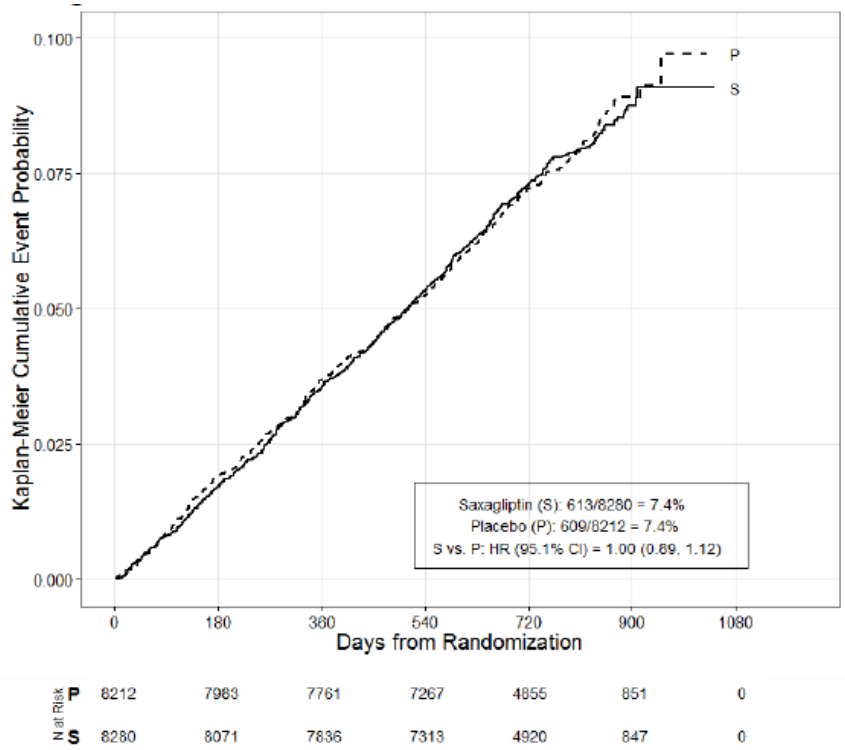
¶ Significance not tested.

Table 13: Major Adverse Cardiovascular Events (MACE) by Treatment Group in the SAVOR Trial

	Saxagliptin		Placebo		Hazard Ratio
	Number of Subjects (%)	Rate per 100 PY	Number of Subjects (%)	Rate per 100 PY	(95.1% CI)
Composite of first event of CV death, non-fatal MI or non-fatal ischemic stroke (MACE)	N=8280	Total PY = 16308.8	N=8212	Total PY = 16156.0	
	613 (7.4)	3.8	609 (7.4)	3.8	1.00 (0.89, 1.12)
CV death	245 (3.0)	1.5	234 (2.8)	1.4	
Non-fatal MI	233 (2.8)	1.4	260 (3.2)	1.6	
Non-fatal ischemic stroke	135 (1.6)	0.8	115 (1.4)	0.7	

The Kaplan-Meier-based cumulative event probability is presented in Figure 2 for time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for both saxagliptin and placebo arms are close together throughout the duration of the trial. The estimated cumulative event probability is approximately linear for both arms, indicating that the incidence of MACE for both arms was constant over the trial duration.

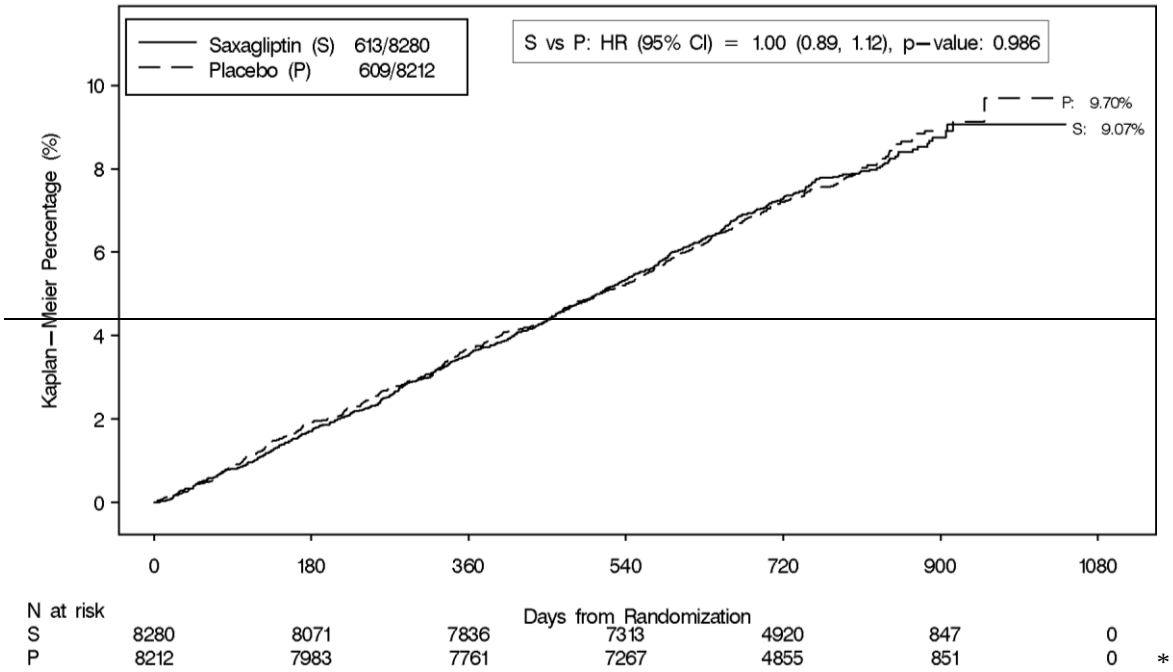
Figure 2: Cumulative Percent of Time to First MACE



Vital status was obtained for 99% of subjects in the trial. There were 798 deaths in the SAVOR trial. Numerically more patients (5.1%) died in the saxagliptin group than in the placebo group (4.6%). The risk of deaths from all cause (Table 14) was not statistically different between the treatment groups (HR: 1.11; 95.1% CI: 0.96, 1.27).

Table 14: All-Cause Mortality by Treatment Group in the SAVOR Study

	Saxagliptin		**Placebo**		**Hazard Ratio**
	Number of Subjects (%)	**Rate per 100 PY**	**Number of Subjects (%)**	**Rate per 100 PY**	**(95.1% CI)**
	N=8280	**PY=16645.3**	**N=8212**	**PY=16531.5**	
All-cause mortality	420 (5.1)	2.5	378 (4.6)	2.3	1.11 (0.96, 1.27)
CV death	269 (3.2)	1.6	260 (3.2)	1.6	
Non-CV death	151 (1.8)	0.9	118 (1.4)	0.7	



Intent-to-treat population

~~Instructions for Local Regulatory Personnel~~: ~~If Kaplan-Meier curve not appropriate for submission, submit the text directly below.~~

~~Events accumulated consistently over time, and the event rates for TRADEMARK and placebo did not diverge notably over time.~~

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

~~No increased risk for the primary endpoint was observed between saxagliptin and placebo in any of the following subgroups: CVD, multiple risk factors for CVD, mild, moderate, or severe renal impairment, age, gender, race, region, duration of type 2 diabetes, history of heart failure, baseline A1C, albumin/creatinine ratio, baseline antidiabetic medication, or baseline use of statins, aspirin, ACE inhibitors, ARBs, beta-blockers, or antiplatelet medications.~~

~~Despite active management of concomitant antidiabetic therapy in both study arms, mean A1C levels were lower in the saxagliptin group compared to the placebo group at Year 1 (7.6% versus 7.9%, difference of −0.35% [95% CI: −0.38, −0.31]) and at Year 2 (7.6% versus 7.9%, difference of −0.30% [95% CI: −0.34, −0.26]). The proportions of subjects with A1C <7% in the saxagliptin group compared to the placebo group were 38% versus 27% at Year 1 and 38% versus 29% at Year 2.~~

~~Compared to placebo, saxagliptin resulted in less need for the initiation of new or increases in current oral diabetes medications or insulin. The improvements in A1C and the proportion of subjects reaching A1C targets among saxagliptin-treated subjects were observed despite lower rates of upward adjustments in diabetes medications or initiation of new diabetes medications or insulin compared with placebo~~

העדכון העיקרי בעלון לצרכן הוא:

<u>. לפני שימוש בתרופה</u>

X אין להשתמש בתרופה אם:

- יש לך תפקוד כלייתי ירוד באופן חמור (הרופא שלך יגדיר מהי רמת הפגיעה בתפקוד הכלייתי שלך)

! אזהרות מיוחדות הנוגעות לשימוש בתרופה

קיים סיכון מוגבר ללקות בחמצת לקטית אם:

- יש לך בעיות חמורות בתפקוד הכליות או שהכליות שלך תחת השפעה של צבע להזרקה או חומר ניגוד לצורך בדיקת הדמיה.
- ~~יש לך בעיות בתפקוד הכליה. אנשים הסובלים מליקוי בתפקוד הכליה, לא אמורים ליטול קומביגלייז XR.~~

3. כשל לבבי, משמעותו שהלב שלך אינו מזרים דם טוב מספיק.

לפני שאתה מתחיל ליטול קומביגלייז XR ספר לרופא אם סבלת בעבר מ:

- כשל לבבי או היו לך בעיות בכליות

פנה מיד לרופא במידה והנך סובל באחד מהסימפטומים הבאים:

- קוצר נשימה מתגבר או קשיי נשימה בייחוד בשכיבה
- נפיחות או בצקות בייחוד בכפות הרגלים, קרסוליים או רגלים.
- עליה מהירה וחריגה במשקל
- עייפות חריגה

סימנים אלו עלולים להיות סימנים לכשל לבבי.

~~כאשר גופך במצבי לחץ כגון חום, טראומה (כגון תאונת דרכים), זיהום או ניתוח, יתכן ויהיה צורך בהתאמת מינון התרופה. יש לעדכן את הרופא אם אחד המצבים האלה חל עליך.~~

לפני הטיפול בקומביגלייז XR ספר לרופא אם:

- **יש לך בעיות בתפקודי הכליות.**

- ~~היה לך בעבר אי פעם אי ספיקת לב או יש לך גורמי סיכון להתפתחות של אי ספיקת לב כמו בעיות בכליה שלך. הרופא שלך יסביר לך על הסימנים של אי ספיקת לב. עליך לפנות מיידית לרופא, רופא או אחות אם הנך מרגיש באחד מסימנים אלו. הסימנים יכולים לכלול גם (לא רק) – קוצר נשימה מתגבר, עליה מהירה במשקל ונפיחות באזור כפות רגליים (בצקת כפות רגליים וקרסול).~~

2. כיצד תשתמש בתרופה?

במידה ויש לך ירידה בתפקודי כליות, ייתכן והרופא ירשום לך מינון נמוך יותר.

4. <u>תופעות לוואי</u>

יש לפנות לרופא בהקדם האפשרי אם הנך מרגיש את התופעות הבאות:

- רמת סוכר נמוכה בדם (היפוגליקמיה): תופעת לוואי זאת עלולה להיות חמורה יותר אצל אנשים שלוקחים תרופות נוספות להורדת הסוכר כמו סולפאנילאוריה או אינסולין. אנא ספר לרופא במידה והנך לוקח תרופות נוספות להורדת סוכר. אם הנך חש בתסמינים של רמות סוכר נמוכות, בדוק את רמות הסוכר, טפל וצור קשר עם הרופא. תסמינים של רמות סוכר נמוכות בדם כוללים: רעד, הזעה, ~~חרדה~~, דופק מהיר, ~~דקירות בשפתיים, חיוורון, טשטוש~~ שינויים בראייה, ~~ערפול או בילבול~~, רעב, כאב ראש, שינוי במצב הרוח.

- כאבים במפרקים. חלק מהאנשים שלוקחים תרופות ממשפחת התרופות של מעכבי ה DPP-4, אליה שייכת גם התרופה קומביגליז XR, עלולים לפתח כאבי מפרקים שיכולים להיות חמורים. צור קשר עם הרופא במידה והנך חדש בכאבי מפרקים חזקים.

- תגובות עוריות. חלק מהאנשים שלוקחים תרופות ממשפחת התרופות של מעכבי ה DPP-4, אליה שייכת גם התרופה קומביגליז XR, עלולים תגובה עורית הנקראת "בולוס פמפיגואיד" bullous pemphigoid העלולה להוביל לקבלת טיפול בבית החולים. ספר לרופא במידה והנך מבחין בשלפוחיות עוריות או הפרדות של שכבת העור החיצונית . ייתכן הרופא יבקש ממך להפסיק טיפול בקומביגליז XR.

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בכבוד רב,
קארין קנבל דובסון

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