

Mediterranean Diet May Be Effective in NAFLD

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

SAN FRANCISCO – The Mediterranean diet may be superior to the low-fat diet for decreasing hepatic fat and increasing insulin sensitivity in patients with nonalcoholic fatty liver disease, based on a small randomized crossover

study conducted in Australia.

After just 6 weeks on the Mediterranean diet, the 12 patients studied had significant improvements in a range of metabolic measures, such as a greater than one-third decrease in hepatic triglyceride content. In contrast, they had no such improvements after 6 weeks on the low-fat diet.

“The Mediterranean diet treats the underlying pathophysiology of NAFLD;

this diet shows promise as a dietary recommendation for NAFLD,” lead author Dr. Marno C. Ryan said at the meeting. “However, this is a small, highly controlled study, and larger, longer-term studies are needed to confirm these findings,” she said.

Importantly, the Mediterranean diet was also well received. “All of our patients enjoyed it, a lot more than the low-fat diet. Our dietitian actually was per-

sonally involved in preparing a lot of the meals,” she explained, noting that a larger trial would require more patient training in food preparation.

Also, cost might be a barrier for some patients in following the Mediterranean diet, said Dr. Ryan of St. Vincent’s Hospital in Melbourne. “Olive oil was a concern, and fish was as well. We did provide patients with money, approximately \$80 a week, for that.”

KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets

Rx ONLY
Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: LACTIC ACIDOSIS

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 lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) should be discontinued and the patient hospitalized immediately. [See Warnings and Precautions.]

INDICATIONS AND USAGE

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. [See Clinical Studies (14) in Full Prescribing Information.]

Important Limitations of Use

KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

KOMBIGLYZE XR has not been studied in combination with insulin.

KOMBIGLYZE XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using KOMBIGLYZE XR. [See Warnings and Precautions.]

CONTRAINDICATIONS

KOMBIGLYZE XR is contraindicated in patients with:

- 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.
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to KOMBIGLYZE XR or saxagliptin, such as anaphylaxis, angioedema, or exfoliative skin conditions. [See Warnings and Precautions and Adverse Reactions.]

WARNINGS AND PRECAUTIONS

Lactic 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. 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 μ g/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 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 radiographic contrast study and for any surgical procedure. [See Warnings and Precautions.]

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]. 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.]

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].

Pancreatitis: There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin. After initiation of KOMBIGLYZE XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, KOMBIGLYZE XR 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 KOMBIGLYZE XR.

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].

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.

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.

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

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

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

Surgical Procedures: Use of KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) 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.

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

Use with Medications Known to Cause Hypoglycemia

Saxagliptin — Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, when used in combination with saxagliptin, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia. [See Adverse Reactions.]

Metformin hydrochloride — Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

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], should be used with caution.

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 reinstated only after renal function has been re-evaluated and found to be normal.

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.

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with saxagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue KOMBIGLYZE XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See Adverse Reactions.]

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with KOMBIGLYZE XR.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other antidiabetic drug.

ADVERSE REACTIONS

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.

Monotherapy and Add-On Combination Therapy

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, placebo-controlled, 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.

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 (72.0% 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 $\geq 5\%$ of patients treated with saxagliptin 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

Table 1: Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Trials* Reported in $\geq 5\%$ 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)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

*The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with saxagliptin 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate $\geq 5\%$ and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in $\geq 2\%$ of patients treated with saxagliptin 2.5 mg or saxagliptin 5 mg and $\geq 1\%$ 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 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.

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

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in $\geq 5\%$ of patients participating in an additional 24-week, active-controlled trial of coadministered saxagliptin and metformin in treatment-naive patients.

Table 2: Coadministration of Saxagliptin and Metformin Immediate-Release in Treatment-Naive Patients: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in $\geq 5\%$ of Patients Treated with Combination Therapy of Saxagliptin 5 mg Plus Metformin Immediate-Release (and More Commonly than in Patients Treated with Metformin Immediate-Release Alone)

	Number (%) of Patients	
	Saxagliptin 5 mg + Metformin* N=320	Placebo + Metformin* N=328
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

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

The investigators are now planning a similar but larger, less well-controlled study in which patients will be followed for 2 years and will have liver biopsy at the beginning and end, she said.

Dr. T. Jake Liang, president of the American Association for the Study of Liver Diseases and chief of the liver diseases branch at the National Institute of Diabetes and Digestive and Kidney Diseases, pointed out that 2%-3% of the U.S. population has NAFLD. That number is likely to increase, he said, given that two-thirds of the population are now overweight.

These new findings are “interesting; further long-term study is warranted,” he said in a press conference. “Obviously, if we can prevent and treat a disease with a diet, that’s probably better than any drugs we can develop.”

Insulin resistance is implicated in the pathogenesis of NAFLD as well as the other components of metabolic syndrome, such as abdominal obesity and dyslipidemia, Dr. Ryan said, giving some background for the study. “Therefore, any therapeutic strategies directed toward NAFLD should also encompass potential benefits for these associated features.”

To be eligible for the study, patients needed to be nondiabetic, with biopsy-proven NAFLD with fibrosis classified as less than F3 in extent, and to consume fewer than two servings of alcohol daily.

The cohort had an equal sex distribution, a mean body mass index of 32 kg/m², and a mean hepatic triglyceride content of 11%.

The patients were randomized to start the study with either the Mediterranean diet or the low-fat, high-carbohydrate diet currently recommended for patients with NAFLD. They ate one diet for 6

weeks, returned to their own diet for 6 weeks as a washout, and then went on the alternative diet for 6 weeks. The aim was to change diet without inducing weight loss, since that can be a confounding factor, Dr. Ryan noted.

All patients received dietary instructions, weekly rotating menus, and approximately 70% of the meals needed for the study diets. They underwent testing – lab assays of fasting blood samples, a 3-hour euglycemic clamp study, and liver imaging and spectroscopy – before and at the end of each 6-week study period.

Patients lost only small amounts of weight on the two diets, an average of 1 kg on the Mediterranean diet and 2.4 kg on the low-fat diet, a nonsignificant difference, Dr. Ryan reported.



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The Mediterranean diet was associated with a 39% reduction in hepatic fat.

The main results showed that the Mediterranean diet was associated with a 39% reduction from baseline in hepatic triglyceride content. This was determined via magnetic resonance spectroscopy after adjustment for weight loss ($P = .001$).

There was a similar reduction in hepatic fat fraction measured by volumetric magnetic resonance imaging ($P = .006$).

The Mediterranean diet was also associated with improvements in insulin sensitivity as determined from reductions in homeostasis model assessment–insulin resistance, or HOMA-IR ($P = .008$) and fasting insulin levels ($P = .003$), and an increase in the glucose infusion rate on the euglycemic clamp study ($P = .09$).

In contrast, the low-fat diet was not associated with significant changes from baseline in any of these measures. “Interestingly, the serum insulin concentration actually increased across the 6-week period of the low-fat diet, presumably in response to the higher carbohydrate intake,” she noted.

When the two diets were directly compared with each other, the Mediterranean diet bested the low-fat diet in terms of changes in hepatic triglyceride content ($P = .03$), insulin levels ($P = .008$), and glucose infusion rate for the euglycemic clamp study ($P = .03$).

Dr. Ryan and Dr. Liang said they had no relevant financial disclosures.

In patients treated with the combination of saxagliptin and metformin immediate-release, either as saxagliptin add-on to metformin immediate-release therapy or as coadministration in treatment-naïve patients, diarrhea was the only gastrointestinal-related event that occurred with an incidence $\geq 5\%$ in any treatment group in both studies. In the saxagliptin add-on to metformin immediate-release trial, the incidence of diarrhea was 9.9%, 5.8%, and 11.2% in the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. When saxagliptin and metformin immediate-release were coadministered in treatment-naïve patients, the incidence of diarrhea was 6.9% in the saxagliptin 5 mg + metformin immediate-release group and 7.3% in the placebo + metformin immediate-release group.

Hypoglycemia: In the saxagliptin clinical trials, adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. The incidence of reported hypoglycemia for saxagliptin 2.5 mg and saxagliptin 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively. In the add-on to metformin immediate-release trial, the incidence of reported hypoglycemia was 7.8% with saxagliptin 2.5 mg, 5.8% with saxagliptin 5 mg, and 5.0% with placebo. When saxagliptin and metformin immediate-release were coadministered in treatment-naïve patients, the incidence of reported hypoglycemia was 3.4% in patients given saxagliptin 5 mg + metformin immediate-release and 4.0% in patients given placebo + metformin immediate-release.

Hypersensitivity Reactions

Saxagliptin — Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received saxagliptin 2.5 mg, 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.

Infections

Saxagliptin — In the unblinded, controlled, clinical trial database for saxagliptin to date, there have been 6 (0.12%) reports of tuberculosis among the 4959 saxagliptin-treated patients (1.1 per 1000 patient-years) compared to 0 reports of tuberculosis among the 2868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with saxagliptin until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of saxagliptin that remained stable throughout saxagliptin treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with saxagliptin use. Causality has not been established and there are too few cases to date to determine whether tuberculosis is related to saxagliptin use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in a saxagliptin-treated patient who developed suspected foodborne fatal salmonella sepsis after approximately 600 days of saxagliptin therapy. There have been no spontaneous reports of opportunistic infections associated with saxagliptin use.

Vital Signs

Saxagliptin — No clinically meaningful changes in vital signs have been observed in patients treated with saxagliptin alone or in combination with metformin.

Laboratory Tests

Absolute Lymphocyte Counts

Saxagliptin — There was a dose-related mean decrease in absolute lymphocyte count observed with saxagliptin. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with saxagliptin 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when saxagliptin 5 mg and metformin were coadministered in treatment-naïve patients compared to placebo and metformin. There was no difference observed for saxagliptin 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤ 750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to saxagliptin although some patients had recurrent decreases upon rechallenge that led to discontinuation of saxagliptin. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. 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 — Saxagliptin did not demonstrate a clinically meaningful or consistent effect on platelet count in the six, double-blind, controlled clinical safety and efficacy trials.

Vitamin B₁₂ Concentrations

Metformin hydrochloride — Metformin may lower serum vitamin B₁₂ concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) and any apparent abnormalities should be appropriately investigated and managed. [See *Warnings and Precautions*.]

Postmarketing Experience: Additional adverse reactions have been identified during postapproval 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.

- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions. [See *Contraindications and Warnings and Precautions*.]
- Acute pancreatitis. [See *Indications and Usage and Warnings and Precautions*.]

DRUG INTERACTIONS

Strong Inhibitors of CYP3A4/5 Enzymes

Saxagliptin — Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., itraconazole, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telitromycin). 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)* in Full Prescribing Information.]

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.

Use with Other Drugs

Metformin hydrochloride — Some medications can predispose to hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving KOMBIGLYZE XR, the patient should be closely observed for loss of glycemic control. When such drugs are withdrawn from a patient receiving KOMBIGLYZE XR, the patient should be observed closely for hypoglycemia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B — 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 hind.

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 7966 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.

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.

Nursing Mothers: No studies in lactating animals have been conducted with the combined components of KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release). 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.

Pediatric Use: Safety and effectiveness of KOMBIGLYZE XR in pediatric patients have not been established.

Geriatric Use: *KOMBIGLYZE XR* — Elderly patients are more likely to have decreased renal function. 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 and Clinical Pharmacology (12.3)* in Full Prescribing Information.]

Saxagliptin — In the six, double-blind, controlled clinical safety and efficacy trials of saxagliptin, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥ 65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride — Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney. Because the risk of lactic acidosis with metformin is greater in patients with impaired renal function, KOMBIGLYZE XR should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. [See *Contraindications, Warnings and Precautions, and Clinical Pharmacology (12.3)* in Full Prescribing Information.]

OVERDOSAGE

Saxagliptin — In a controlled clinical trial, once-daily, orally-administered saxagliptin in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient’s clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

Metformin hydrochloride — Its overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions*]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdose is suspected.

PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide in Full Prescribing Information.

Instructions

Patients should be informed of the potential risks and benefits of KOMBIGLYZE XR and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

The risks of lactic acidosis due to the metformin component, its symptoms and conditions that predispose to its development, as noted in Warnings and Precautions (5.1), should be explained to patients. Patients should be advised to discontinue KOMBIGLYZE XR immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgia, malaise, unusual somnolence, dizziness, slow or irregular heart beat, sensation of feeling cold (especially in the extremities), or other nonspecific symptoms occur. Gastrointestinal symptoms are common during initiation of metformin treatment and may occur during initiation of KOMBIGLYZE XR therapy; however, patients should consult their physician if they develop unexplained symptoms. Although gastrointestinal symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to lactic acidosis or other serious disease.

Patients should be counseled against excessive alcohol intake while receiving KOMBIGLYZE XR.

Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with KOMBIGLYZE XR.

Patients should be informed that acute pancreatitis has been reported during postmarketing use of saxagliptin. Before initiating KOMBIGLYZE XR, patients should be questioned about other risk factors for pancreatitis, such as a history of pancreatitis, alcoholism, gallstones, or hypertriglyceridemia. Patients should also be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue KOMBIGLYZE XR and contact their physician if persistent severe abdominal pain occurs [see *Warnings and Precautions*].

Patients should be informed that the incidence of hypoglycemia may be increased when KOMBIGLYZE XR is added to an insulin secretagogue (e.g., sulfonylurea).

Patients should be informed that serious allergic (hypersensitivity) reactions, such as angioedema, anaphylaxis, and exfoliative skin conditions, have been reported during postmarketing use of saxagliptin. If symptoms of these allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking KOMBIGLYZE XR and seek medical advice promptly.

Patients should be informed that KOMBIGLYZE XR must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet. Patients should be informed that if they miss a dose of KOMBIGLYZE XR, they should take the next dose as prescribed, unless otherwise instructed by their healthcare provider. Patients should be instructed not to take an extra dose the next day.

Healthcare providers should instruct their patients to read the Medication Guide before starting KOMBIGLYZE XR therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their healthcare provider if they develop any unusual symptom or if any existing symptom persists or worsens.

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