

## NEW DRUG UPDATE

<b>Drug Name:</b>	saxagliptin and metformin extended-release (ER)
<b>Trade Name (Manufacturer):</b>	Kombiglyze™ XR (BMS/AZ)
<b>Form:</b>	Tablet (fixed combination)
<b>Strength:</b>	2.5 mg/1,000 mg, 5 mg/500 mg, 5 mg/1,000 mg
<b>FDA Approval:</b>	November 08, 2010
<b>Market Availability:</b>	Mid-November 2010
<b>FDA Approval Classification:</b>	Standard review
<b>Classification:</b>	Antihyperglyc (DPP-4) Inhibitor & Biguanide Comb (C4F)

**Indication:**<sup>1</sup> Kombiglyze XR, a combination of the dipeptidyl peptidase-4 (DPP-4) inhibitor, saxagliptin, and the biguanide, metformin, 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.

**Contraindications/Warnings:** Kombiglyze XR carries a boxed warning for lactic acidosis. It is contraindicated in metabolic acidosis, including diabetic ketoacidosis. It is contraindicated in renal impairment (e.g., serum creatinine levels  $\geq 1.5$  mg/dL for men,  $\geq 1.4$  mg/dL for women, or abnormal creatinine clearance). Renal function should be monitored before initiation and at least annually. Kombiglyze XR is not indicated for the treatment of type 1 diabetes or diabetic ketoacidosis. Patients should be warned against excessive alcohol intake. It has not been studied in combination with insulin. Kombiglyze XR should be temporarily discontinued in patients undergoing radiologic testing involving intravascular administration of iodinated contrast materials due to potential acute alteration of renal function. It is not recommended in hepatic impairment as lactic acidosis has occurred in some patients. Kombiglyze XR should be discontinued for surgical procedures that require restricted food and fluid intake. Metformin may lower vitamin B12 levels therefore caution is warranted in patients with vitamin B12 deficiency. If used in combination with an insulin secretagogue (e.g. sulfonylurea) a lower dose of the sulfonylurea may be needed to reduce the risk of hypoglycemia. There are no conclusive macrovascular outcomes with Kombiglyze XR or any other antidiabetic agent.

**Drug Interactions:** Coadministration with strong CYP3A4/5 inhibitors particularly ketoconazole but including atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin, significantly increases saxagliptin concentrations. The dose of Kombiglyze XR should be limited to 2.5 mg/1000 mg once daily. Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, cimetidine, ranitidine, triamterene, trimethoprim, or vancomycin) eliminated by renal tubular secretion can reduce the elimination of metformin therefore caution is warranted.

**Common Adverse Effects:** The most common adverse reactions (> five percent and more common than placebo) in patients taking metformin ER include diarrhea and nausea/vomiting. The most common adverse reactions ( $\geq$  five percent and more common than placebo) in patients taking saxagliptin include upper respiratory tract infection, urinary tract infection, and headache. Adverse reactions reported in  $\geq 5$  percent of treatment-naive patients treated with coadministered saxagliptin and metformin and more commonly than in patients treated with metformin alone are: headache and nasopharyngitis.

**Special Populations:**

**Pediatrics:** The safety and effectiveness of Kombiglyze XR have not been established in pediatric patients.

**Pregnancy:** Pregnancy Category B.

**Geriatrics:** Elderly patients are more likely to have decreased renal function. Since metformin is contraindicated in patients with renal impairment, carefully monitor renal function in geriatrics and use Kombiglyze XR with caution as age increases. No dosage adjustment is recommended based on age alone.

**Renal Impairment:** Due to the metformin component, Kombiglyze XR is contraindicated in patients with renal impairment

**Hepatic Impairment:** Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Kombiglyze XR is not recommended in patients with hepatic impairment.

**Dosages:** Administer once daily with the evening meal. Individualize the starting dose based on the patient's current regimen then adjust the dose based on effectiveness and tolerability.

The recommended starting dose in patients who need 5 mg of saxagliptin and who are not currently treated with metformin is 5 mg saxagliptin/500 mg metformin ER once daily with gradual dose escalation to reduce the gastrointestinal (GI) adverse effects of metformin.

In patients already treated with metformin, the dose should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose. If switching from metformin immediate-release to metformin extended-release, glycemic control should be closely monitored and dosage adjustments made. Patients who need 2.5 mg saxagliptin in combination with metformin ER may be treated with Kombiglyze XR 2.5 mg/1,000 mg. Patients who need 2.5 mg saxagliptin who are either metformin naive or who require a dose of metformin higher than 1,000 mg should use the individual components.

The maximum daily dose is 5 mg saxagliptin/2,000 mg metformin ER. The tablet should not be crushed, cut, or chewed.

For patients also taking strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole) limit the saxagliptin dose to 2.5 mg daily.

No studies have specifically examined the safety and efficacy of Kombiglyze XR in patients previously treated with other antidiabetic agents and switched to Kombiglyze XR. Sometimes, the inactive ingredients of Kombiglyze XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

**Clinical Trials:** A literature search was performed using "metformin ER" and "saxagliptin". Placebo-controlled trials were included in the absence of comparative trials.

Approval of Kombiglyze XR was based on two randomized, double-blind, 24-week, active-controlled clinical trials (n=1306 and n=743, respectively) of saxagliptin and metformin immediate-release (IR), administered as separate tablets, compared with metformin IR

monotherapy.<sup>2,3,4</sup> In the first study patients were treatment naïve. In the second study patients were on a stable dose of metformin for at least eight weeks.

In the treatment-naïve study saxagliptin 5 mg and metformin IR significantly decreased mean hemoglobin (Hb) A1c levels from baseline compared with metformin IR alone (-2.5 percent versus -2 percent;  $p < 0.0001$ ), significantly increasing the proportion of patients achieving A1c levels < 7 percent (60 percent versus 41 percent;  $p < 0.05$ ). There were also statistically significant reductions in mean fasting plasma glucose and two-hour postprandial glucose levels (-60 mg/dL versus -47 mg/dL [ $p < 0.05$ ] and -138 mg/dL versus -97 mg/dL [ $p < 0.05$ ], respectively).

In the second study the addition of saxagliptin 2.5 mg and 5 mg to metformin IR in patients who were not controlled on metformin monotherapy significantly decreased mean Hb A1c levels from baseline by 0.6 percent and 0.7 percent, respectively, compared with an increase of 0.1 percent with metformin monotherapy ( $p < 0.0001$  for both). Both doses resulted in a significant increase in the proportion of patients with Hb A1c levels below 7 percent (37 percent and 44 percent versus 17 percent;  $p < 0.05$  for both comparisons). There were also statistically significant reductions in fasting plasma glucose and two-hour postprandial glucose levels (-14 mg/dL and -22 mg/dL versus +1 mg/dL [ $p < 0.05$ ]; -62 mg/dL and -58 mg/dL versus -18 mg/dL [ $p < 0.05$ ], respectively).

No clinical efficacy or safety studies have been conducted specifically with saxagliptin and metformin ER. Metformin ER and IR tablets have a similar rate of absorption (as measured by area under the curve); peak plasma levels of metformin ER are about 20 percent lower than those of the IR tablets at the same dose.

Results of a 24-week, randomized, double-blind study suggest that patients receiving metformin IR therapy may safely be switched to once daily metformin ER at the same total dose, up to 2,000 mg once daily.

A 4-week, randomized, double-blind, placebo-controlled, multicenter study compared saxagliptin 5 mg once daily in combination with a stable dose of metformin ER versus placebo in combination with metformin ER in 93 patients with type 2 diabetes who were inadequately controlled with stable doses of metformin IR or metformin ER  $\geq 1,500$  mg/day.<sup>5</sup> The reduction from baseline in 24-hour MWG (primary outcome) was significantly greater for saxagliptin 5 mg + metformin ER (-13.8 mg/dL; -0.77 mmol/L) compared with placebo/metformin ER (3 mg/dL; 0.17 mmol/L) ( $p = 0.0001$ ). Saxagliptin 5 mg and metformin ER also resulted in significant mean reductions from baseline in four-hour mean weighted postprandial glucose (PPG), two-hour PPG, three-day average mean daily glucose, and fasting plasma glucose levels compared with placebo plus metformin ER ( $p \leq 0.001$ ).

An 18-week, double-blind, multicenter, noninferiority trial compared the efficacy and safety of saxagliptin and sitagliptin, in adults with type 2 diabetes ( $n = 801$ ) patients with inadequate glycemic control on metformin.<sup>6</sup> Patients with Hb A1c 6.5-10 percent on stable metformin doses (1500-3000 mg/day) were randomized 1:1 to add-on 5 mg saxagliptin or 100 mg sitagliptin once daily for 18 weeks. The primary efficacy analysis was a comparison of the change from baseline Hb A1c at week 18 in per-protocol patients. The adjusted mean changes in Hb A1c following the addition of saxagliptin or sitagliptin to stable metformin therapy were -0.52 and -0.62 percent, respectively. The between-group difference was 0.09% (95% confidence interval, -0.01 to 0.20 percent), indicating noninferiority. Both treatments were generally well tolerated. The incidence and types of side effects were comparable between groups. Hypoglycemic events were mostly

mild and reported in approximately three percent of patients in each treatment group. In both groups, body weight declined by a mean of 0.4 kg.

**Other Drugs Used for Condition:** Other drugs that are used for the management of type 2 diabetes mellitus are sulfonylureas (Diabeta<sup>®</sup>, Glynase<sup>®</sup> PresTab<sup>®</sup>, Micronase<sup>®</sup> Glucotrol XL<sup>®</sup> Glucotrol<sup>®</sup>, Amaryl<sup>®</sup>); metformin (Glucophage<sup>®</sup>, Glucophage XR<sup>®</sup>, Glumetza<sup>™</sup>, Fortamet<sup>™</sup>, Riomet<sup>™</sup>) and metformin combination products (Glucovance<sup>®</sup>, Glucovance<sup>®</sup>); meglitinides (Starlix<sup>®</sup>, Prandin<sup>®</sup>); TZDs (Actos<sup>®</sup>, Avandia<sup>®</sup>, Duetact<sup>™</sup>, Avandaryl<sup>®</sup>, Actoplus Met<sup>™</sup>, Avandamet<sup>®</sup>); DPP-4 Inhibitors (Onglyza<sup>™</sup>, Januvia<sup>™</sup>, Janumet<sup>™</sup>); insulin mimetics and enhancers (Byetta<sup>™</sup>, Symlin<sup>®</sup>); alpha-glucosidase inhibitors (Precose<sup>®</sup>, Glyset<sup>®</sup>); and insulin.

**Place in Therapy:** Kombiglyze XR offers a fixed dose combination of saxagliptin and metformin in adults with type 2 diabetes. Single ingredients of this product are available as saxagliptin (Onglyza) and metformin ER. The combination tablet offers the convenience of a single table and potential increased compliance. Janumet, combination of sitagliptin and metformin, is the only other combination DPP-4/biguanide. Although the fixed dose combinations have not been compared, a single ingredient study showed non-inferiority for saxagliptin and metformin versus sitagliptin and metformin.

## References

<sup>1</sup> Kombiglyze XR [package insert]. Princeton, NJ; BMS; November 2010.

<sup>2</sup> Madzinsky M, Pfutzner A, Paz-Pacheco E, et al. For the CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obesity Metabolism*. 2009; 11:611-622.

<sup>3</sup> Defonzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care*. 2009; 32:1649-1655.

<sup>4</sup> Kombiglyze XR [package insert]. Princeton, NJ; BMS; November 2010.

<sup>5</sup> Stenlof K, Raz I, Neutel J, et al. Saxagliptin and metformin XR combination therapy provides glycemic control over 24 hours in patients with T2DM inadequately controlled with metformin. *Curr Med Res Opin*. 2010; 26(10): 2355-2363.

<sup>6</sup> Sheen AJ, Charpentier G, Ostgren CJ, et al. Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev*. 2010; 26(7):540-549.