

said, laying out the rationale for the trial. Flaxseed is an annual plant, rich in lignans, which are a major class of phytoestrogens, she said. It is thought to have a weak estrogenlike effect, as well as estrogen antagonist effect.

In 2005, a pilot study was conducted in 30 women. They were given 400 mg of ground flaxseed, and investigators reported a 57% reduction in hot flash scores and a 50% reduction in hot flash frequency. This led to the current trial, said Dr. Pruthi.

To be eligible, women with or without a history of breast cancer had to have

more than 28 hot flashes per week. In all, 188 women were enrolled and 178 were



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DR. PRUTHI

randomized (88 to flaxseed bars containing 410 mg of lignans and fiber, and

90 to placebo bars containing protein and fiber, but no flaxseed, soy, or lignans). For 6 weeks, the participants were to eat one bar per day. The primary end point was a change from baseline in hot flash scores at week 6.

Of the entire group, 91 had a history of breast cancer but were without active disease. This group included women who were being treated with an aromatase inhibitor or tamoxifen.

Mean hot flash scores decreased by 4.9 units (33%) in the flaxseed arm, and 3.5 (29%) in the placebo arm ( $P = .29$ ). "There was no significant difference in

the reduction of hot flash scores between the two arms," said Dr. Pruthi.

No statistically significant toxicity differences were experienced between study arms, but both groups reported substantial abdominal distention, gas, diarrhea, and nausea.

Although the results were disappointing, the trial does not leave women without remedies for hot flashes. Dr. Pruthi noted that venlafaxine and gabapentin were effective, and had been studied in randomized, placebo-controlled trials. "However, there are side effects with those drugs. Patients need to balance between treating their symptoms and managing their side effects, which is why we need to do more studies in other complementary therapies," she said.

**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.

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-naive 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-naive 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-naive 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 no 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-naive 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  $\leq 750$  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 B<sub>12</sub> Concentrations**  
*Metformin hydrochloride*  
Metformin may lower serum vitamin B<sub>12</sub> 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*.]

**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., 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)* 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 (saxagliptin and metformin HCl extended-release) 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 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  $\geq 1629$  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. 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  $\geq 65$  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*  
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.

Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA  
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# Denosumab Not Cost Effective in Some Cancers

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY

CHICAGO – Denosumab, a drug newly approved for prevention of skeletal-related adverse events in cancer patients with bone metastases from solid tumors, is not cost effective when compared with zoledronic acid in patients with breast or prostate cancers, according to a pair of pharmacoeconomic analyses.

A review of data from a key phase III trial in 2,046 patients with metastatic breast cancer found the cost per quality-adjusted life-year (QALY) gained with denosumab (Xgeva) was \$643,726 when compared with zoledronic acid (Zometa), John A. Carter and his coinvestigators reported in a poster at the meeting.

This ratio is far higher than the \$50,000 to \$100,000 that is considered to be good value for a medical intervention, they said.

A related study in castration-resistant prostate cancer metastatic to the bone found even more substantial cost differentials. The resultant cost per QALY for denosumab would be about \$1.25 million in this setting, reported Sonya H. Snedecor, Ph.D., and her coauthors in a separate poster.

In both studies, investigators attributed the high cost per QALY to the higher drug acquisition cost of denosumab combined with limited added prevention of skeletal-related events (SREs) and a lack of overall survival or disease progression benefits for denosumab vs. zoledronic acid. "What we found [in the prostate cancer study] is that there were very little gains in quality-adjusted life-years with the use of denosumab – very, very minuscule, about five per thousandths of a year," Marc Botteman of Pharmert North America, said in an interview.

Novartis, the maker of zoledronic acid, sponsored both studies. Mr. Carter and Dr. Snedecor disclosed consultant or advisory roles with Novartis. One of their coauthors was a Novartis employee with stock ownership.

–Richard Hyer