

Propoxyphene Yanked Due to Arrhythmia Risk

BY LORINDA BULLOCK

FROM AN FDA TELECONFERENCE

Propoxyphene, a widely used treatment for mild to moderate pain, has been removed from the U.S. market because of an increased risk of serious fatal heart rhythm abnormalities in people taking the drug, Food and Drug Administration officials said Nov. 19.

During a teleconference, health care providers were advised to stop prescribing the drugs known by the brand names Darvon and Darvocet immediately.

"The trial showed that propoxyphene significantly increased the QT interval, which is one measure of the heart's electrical activity. This effect was seen in normal volunteers at propoxyphene doses at or slightly above the maximum recommended doses in the approved labeling," said Dr. John Jenkins, director of the Office of New Drugs at the FDA's Center for Drug Evaluation and Research (CDER).

Dr. Jenkins said that an increase in the QT interval of the magnitude seen with propoxyphene is known to increase the risk that patients may suffer potentially serious or even fatal heart rhythm abnormalities. "What is unique here is the

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new heart data show that adverse effects occur in regular doses in normal volunteers and not just in overdose."

The new data from the clinical trial also showed that propoxyphene increased the duration of two other measures of the heart's electrical activity – the PR interval and the QRS complex. Increases in these measures also are known to lead to abnormalities in heart rhythm, Dr. Jenkins said.

Since 1978, two citizen petitions have asked the agency to either ban the drug or reschedule it from Schedule IV to Schedule II. The agency did not act on the petitions until July 2009, when it required the manufacturer of Darvon and Darvocet, Xanodyne Pharmaceuticals Inc., to conduct a new safety study of the drug in healthy volunteers.

The new data altered the agency's assessment of the risk-benefit profile of the drug by showing that the heart risk of propoxyphene could apply to all users and not just those who took excessive doses or those with medical conditions that might reduce their ability to clear propoxyphene from the body, Dr. Jenkins said.

"Since it is not possible to accurately predict what patients might be at risk or to monitor patients while on the drug for signs of an increased risk, we concluded that a risk evaluation and mitigation strategy or REMS would not be appro-

priate in this case," Dr. Jenkins said.

At the agency's request, Xanodyne voluntarily removed its drugs from store shelves Nov. 18. The FDA has requested that manufacturers of the approved generic versions of propoxyphene do the same.

In 2009, an estimated 10 million people were taking some form of propoxyphene – usually in a formulation that also contains acetaminophen (such as Darvocet), said Dr. Gerald Dal Pan, di-

rector of the FDA's Office of Surveillance and Epidemiology at CDER. Patients taking the drug are advised not to stop treatment immediately. Instead, they should discuss with their physicians safely switching to another treatment. If propoxyphene is stopped suddenly, Dr. Dal Pan said, withdrawal symptoms such as nausea, vomiting, diarrhea, anxiety, and shivering may occur. Once the drug is cleared from the body, the heart risks

go away, so longtime users should not fear that they are more vulnerable to heart arrhythmias, he said.

Internationally, regulatory agencies have already banned propoxyphene. The FDA's original approval of propoxyphene in 1957 was based on older safety standards and did not include "the careful assessment of the possible effects on the electroactivity of the heart that is required for all new drugs today," Dr. Jenkins said. ■

Now Approved

In addition to diet and exercise to improve glycemic control in your adult patients with type 2 diabetes when treatment with both saxagliptin and metformin is appropriate

ONCE A DAY
kombiglyze XR
(saxagliptin and metformin HCl
extended-release) tablets

The first and only once-a-day
metformin XR + DPP-4 inhibitor*
combination tablet.

ONE DAILY DOSE

Generally taken once-daily with evening meal; gradually titrate dose to reduce GI side effects associated with metformin. Maximum daily recommended dose is 5 mg saxagliptin and 2000 mg metformin XR that can be taken as two 2.5 mg/1000 mg tablets once a day.

*saxagliptin

Indication and Important Limitations of Use

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.

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.

Important Safety Information

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 should be discontinued and the patient hospitalized immediately. [See Warnings and Precautions]

Contraindications

- Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or abnormal creatinine clearance)
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- KOMBIGLYZE XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function.

Warnings and Precautions

- The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years). When it occurs, it is fatal in approximately 50% of cases. Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency.
- 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.
- Lactic acidosis risk increases with the degree of renal dysfunction and patient age. The risk may be significantly decreased by use of minimum effective dose of metformin and regular monitoring of renal function. Careful renal monitoring is particularly important in the elderly. KOMBIGLYZE XR should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- Withhold KOMBIGLYZE XR in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

- Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal.
- KOMBIGLYZE XR is not recommended in patients with hepatic impairment.
- Metformin may lower vitamin B12 levels. Measure hematological parameters annually.
- Warn patients against excessive alcohol intake.
- KOMBIGLYZE XR should be suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until patient's oral intake has resumed and renal function is normal.
- Use of saxagliptin or metformin with medications known to cause hypoglycemia – Saxagliptin: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if used in combination with KOMBIGLYZE XR. – Metformin: 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, during concomitant use with other glucose-lowering agents (such as sulfonylureas or insulin), or with use of ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.
- 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. KOMBIGLYZE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours after the procedure and reinstated only after renal function is normal.
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other anti-diabetic drug.

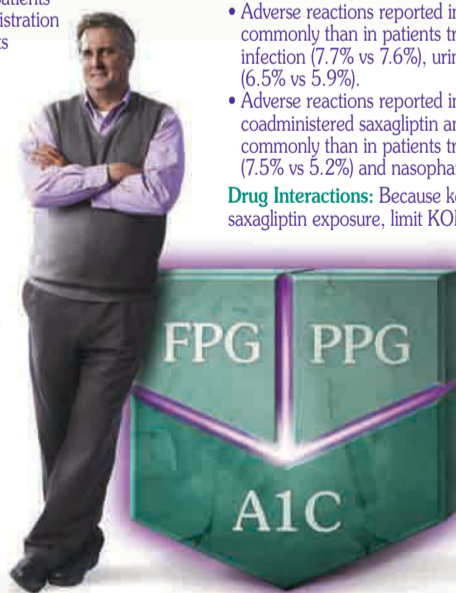
Adverse Reactions

- Adverse reactions reported in $>5\%$ of patients treated with metformin extended-release and more commonly than in patients treated with placebo were: diarrhea (9.6% vs 2.6%) and nausea/vomiting (6.5% vs 1.5%).
- Adverse reactions reported in $\geq 5\%$ of patients treated with saxagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (7.7% vs 7.6%), urinary tract infection (6.8% vs 6.1%), and headache (6.5% vs 5.9%).
- Adverse reactions reported in $\geq 5\%$ of treatment-naïve patients treated with coadministered saxagliptin and metformin immediate-release (IR) and more commonly than in patients treated with metformin IR alone were: headache (7.5% vs 5.2%) and nasopharyngitis (6.9% vs 4.0%).

Drug Interactions: Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, limit KOMBIGLYZE XR to 2.5 mg/1000 mg once daily when coadministered with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

Use in Specific Populations

- **Pregnant and Nursing Women:** There are no adequate and well-controlled studies in pregnant women. KOMBIGLYZE XR should be used during pregnancy only if clearly needed. 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 Patients:** Safety and effectiveness of KOMBIGLYZE XR in pediatric patients have not been established.



Please see adjacent Brief Summary of US Full Prescribing Information including **Boxed WARNING** about lactic acidosis.

Bristol-Myers Squibb

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