DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Henry A. McKinnell, Jr., Ph.D.
Chairman of the Board and Chief Executive Officer
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Re: NDA 21-130; 21-131; 21-132
ZYVOX® (linezolid) injection, tablets, and oral suspension
MACMIS # 13544

WARNING LETTER

Dear Dr. McKinnell:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional journal advertisement (ad) for ZYVOX® (linezolid) injection, tablets, and oral suspension, submitted by Pfizer, Inc. under cover of Form FDA 2253. The ad presents an unsubstantiated implied superiority presentation, broadens the indication for ZYVOX®, fails to reveal important risk information associated with the use of ZYVOX®, and lacks fair balance. Therefore, the ad misbrands the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. 21 U.S.C. 352(n) & 321(n); 21 CFR 202.1(e)(5)(iii); (e)(6)(i); (e)(7)(viii). Your misleading promotion of ZYVOX®, and in particular, your unsubstantiated implied claims regarding its superiority to vancomycin, poses serious public health and safety concerns because of its potential to result in the inappropriate use of ZYVOX®, which is associated with increased toxicity relative to vancomycin.

Background

With respect to the nosocomial pneumonia indication, the Indications and Usage section of the approved product labeling (PI) for ZYVOX®states (in part):

> ZYVOX® formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and-resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX® and other antibacterial drugs, ZYVOX® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

ZYVOX® is associated with serious risks, as described in the Bolded Warnings, Bolded Precautions, and Precautions sections of the PI:

WARNINGS
Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.

PRECAUTIONS
General
Lactic acidosis has been reported with the use of ZYVOX®. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX® should receive immediate medical evaluation.

Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX® and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions).

ZYVOX® has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

The safety and efficacy of ZYVOX® formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

> Peripheral and optic neuropathy have been reported in patients treated with ZYVOX®, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration.
>
> If symptoms of visual impairment appear, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. If peripheral or optic neuropathy occurs, the continued use of ZYVOX® in these patients should be weighed against the potential risks.

Implied Superiority Claim

Your ad implies that ZYVOX® is superior to vancomycin for the treatment of nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Specifically, your ad presents a graph with the header "Two identical, randomized, double-blind, and prospective studies were retrospectively analyzed." The graph presents the clinical cure rate of nosocomial pneumonia in three populations treated with ZYVOX® or vancomycin: clinically evaluable; *S. aureus*; and MRSA. The MRSA population shows a p-value of <0.01 in favor of ZYVOX® compared to vancomycin, indicating that ZYVOX® is superior to vancomycin in treatment of MRSA.

The data supporting the implied superiority claim do not constitute substantial evidence or substantial clinical experience. The studies you present in the ad are not two adequate and well-controlled studies, but rather one study that was conducted prior to marketing and continued as a post-marketing study. Furthermore, the presentation in the ad is based on a post-hoc subgroup analysis; p-values are meaningless in this situation and cannot be used to demonstrate statistically significant differences between treatment groups. When looking for differences between treatment groups, the study must be designed to look for these differences prospectively, and must be sufficiently powered. The studies you present in the ad were not designed in this way.

This presentation therefore is misleading because it implies that ZYVOX® is superior to vancomycin for the treatment of nosocomial pneumonia caused by MRSA when this has not been demonstrated by substantial evidence or substantial clinical experience. The Clinical Studies section of ZYVOX®'s PI for the treatment of nosocomial pneumonia states: "The cure rates in clinically evaluable patients were 57% for linezolid-treated patients and 60% for vancomycin-treated patients." Furthermore, Table 16 of the PI presents the cure rates by pathogen for microbiologically evaluable patients. The cure rate presented for nosocomial pneumonia isolated MRSA infection is 59% (13/22) for ZYVOX® and 70% (7/10) for vancomycin.

Broadening of Indication

Your ad implies that ZYVOX® is approved for the treatment of all infections caused by MRSA.

For example, the following claim appears as a headline on page 3 of your ad:

- "MRSA meets its match"

This claim is misleading because it implies that ZYVOX® is useful in all infections caused by MRSA, a broader range of conditions than is approved in its PI, when this has not been demonstrated by substantial evidence or substantial clinical experience. According to the PI, the two specific MRSA indications approved for ZYVOX® are for the treatment of nosocomial pneumonia and complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis. We note that page 3 of your ad includes the following statement: "ZYVOX® is indicated in the treatment of nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and-resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms." However, inclusion of this important contextual information in very small type size at the bottom of the third page of the ad does not correct the misleading suggestion conveyed by the ad as a whole that ZYVOX® is indicated for the treatment of all MRSA infections.

Failure to Reveal Important Risk Information

The ad misleadingly fails to reveal facts that are material in light of representations made with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the main part of the ad presents effectiveness claims for ZYVOX®, such as "A PROVEN THERAPY DESERVES A CLOSER LOOK," "SERIOUS INFECTION; SERIOUS RESULTS," and "MRSA meets its match," but fails to reveal important risk information associated with the use of ZYVOX®. For example, you fail to include all the relevant risk information from your bolded warning concerning the risk of myelosuppression. Specifically, you fail to mention that "**Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression**."

In addition, you fail to include the bolded precautions regarding risk of lactic acidosis and spontaneous reports of serotonin syndrome. Specifically, the PI states "**Lactic acidosis has been reported with the use of ZYVOX®. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX® should receive immediate medical evaluation" and "Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX® and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions)."**

The ad also fails to include additional precautions regarding peripheral and optic neuropathy. Furthermore, the ad fails to reveal the important risk information and limitations on use that were added to the labeling of all antibiotics per the antibiotic labeling rule, 21 CFR 201.24.

Lack of Fair Balance

Your ad fails to present the risk information with a prominence and readability reasonably comparable to the presentation of effectiveness information. Throughout the three main pages of the four page journal ad effectiveness claims for ZYVOX® are presented using large, colorful, bolded headers as well as a colorful chart, and with a significant amount of white space. In contrast, all of the risk information is relegated to page three of the four page piece and is presented in very small font in a single-spaced paragraph at the bottom of the page, below the indications for use, without additional presentation elements that indicate to the reader that it is important risk information.

Conclusion and Requested Action

Your ad presents an unsubstantiated implied superiority claim, broadens the indication for ZYVOX®, fails to reveal important risk information associated with the use of ZYVOX®, and lacks fair balance. The ad therefore misbrands your drug in violation of the Act (21 U.S.C. 352(n) & 321(n)) and FDA implementing regulations. 21 CFR 202.1(e)(5)(iii); (e)(6)(i); (e)(7)(viii).

DDMAC requests that Pfizer immediately cease the dissemination of violative promotional materials for ZYVOX® such as those described above. Please submit a written response to this letter on or before August 3, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for ZYVOX® such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42 Room 8B-45, 5600 Fishers Lane, Rockville MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 13544 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for ZYVOX® comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melissa Moncavage
7/20/05 04:32:55 PM
Signed for Thomas Abrams