DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

TRANSMITTED BY FACSIMILE **May 26, 2006**

Enna Krivitsky
Associate Director, Regulatory Affairs
Sandoz, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413

Re: ANDA 75-932
Bupropion hydrochloride extended-release tablets (SR)
MACMIS 14211

Dear Ms. Krivitsky:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional print advertisement for bupropion hydrochloride extended-release tablets (SR), submitted by Sandoz, Inc. (Sandoz) under cover of Form FDA 2253. This promotional piece is violative because it has the form of a reminder advertisement for a drug whose labeling contains a boxed warning relating to a serious hazard associated with the use of the drug product. Because the reminder format was used, the print ad fails to include information in brief summary relating to side effects, contraindications, and effectiveness as required by regulation. Thus, the print advertisement misbrands bupropion hydrochloride extended-release tablets (SR) in violation of Sections 502(n) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(n) and 321(n) and FDA's implementing regulations 21 C.F.R. §§ 202.1(e)(1), (e)(2)(i), (e)(3).

Background

According to its FDA-approved product labeling (PI), bupropion hydrochloride extended-release tablets (SR) is approved for the following indication (in pertinent part):

> Bupropion hydrochloride extended-release tablets (SR) are indicated for the treatment of depression. The efficacy of bupropion in the treatment of depression was established in two 4-week controlled trials of depressed inpatients and in one 6-week controlled trial of depressed outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL PHARMACOLOGY).

The use of bupropion hydrochloride extended-release tablets (SR) is associated with a boxed

warning. Specifically, the PI states:

BOXED WARNING

Suicidality in Children and Adolescents
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Bupropion Hydrochloride Extended-release Tablets (SR) or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are stared on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Bupropion Hydrochloride Extended-release Tablets (SR) is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use)

Pooled analysis of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Violative "Reminder Ad"

According to 21 C.F.R. § 202.1(e)(2)(i) (in pertinent part), "Reminder advertisements . . . are not permitted for a prescription drug product whose labeling contains a boxed warning relating to a serious hazard associated with the use of the drug product." Therefore, because the labeling for bupropion hydrochloride extended-release tablets (SR) contains a boxed warning related to a serious hazard associated with the use of the drug product, it is a violation to present this drug product in promotional material that takes the form of a reminder advertisement.

All advertisements for any prescription drug, unless otherwise exempt (such as permissible reminder advertisements), must include a true statement of information in brief summary relating to side effects, contraindications (including side effects, warnings, precautions, and contraindications, etc.), and effectiveness as required by regulation. (See 21 U.S.C. § 352(n), 21 C.F.R. §§ 202.1(e)(1), (e)(3)) This print advertisement fails to present such a brief summary.

Conclusion and Requested Action

Your promotional piece is in the form of an impermissible reminder advertisement that also fails to include information in brief summary relating to side-effects, contraindications, and

effectiveness for bupropion hydrochloride extended-release tablets (SR) in violation of 21 U.S.C. §§ 352(n), 321(n); 21 C.F.R. §§ 202.1(e)(1), (e)(2)(i), (e)(3).

DDMAC requests that Sandoz immediately cease the dissemination of violative promotional materials for bupropion hydrochloride extended-release tablets (SR) such as those described above. Please submit a written response to this letter on or before June 12, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for bupropion hydrochloride extended-release tablets (SR) such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at (301) 796-9878. In all future correspondence regarding this matter, please refer to MACMIS# 14211 in addition to the ANDA 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 bupropion hydrochloride extended-release tablets (SR) comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

Thomas Abrams for

Catherine B. Gray, PharmD
Acting Group Leader
Division of Drug Marketing,
Advertising, and Communications