DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Joseph P. Pieroni, President
Daiichi Sankyo, Inc.
Two Hilton Court
Parsippany, NJ 07054

RE: NDA # 20-989
Evoxac Capsules (cevimeline hydrochloride)
MACMIS ID # 14792

WARNING LETTER

Dear Mr. Pieroni:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a wall calendar (DSEV06-0028) and dry erase board (DSEV06-0029) for Evoxac Capsules (cevimeline hydrochloride) (Evoxac) submitted by Daiichi Sankyo, Inc. (Daiichi) under cover of Form FDA 2253. These promotional materials are false or misleading because they present efficacy claims for Evoxac but fail to communicate information about the risks associated with its use. Thus, your wall calendar and dry erase board misbrand Evoxac in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) and 321(n**).**

Background

According to the approved product labeling (PI):

> Cevimeline is indicated for the treatment of symptoms of dry mouth in patients with Sjögren's Syndrome.

The PI also includes the following risk information (in pertinent part):

> **CONTRAINDICATIONS**
> Cevimeline is contraindicated in patients with uncontrolled asthma, known hypersensitivity to cevimeline, and when miosis is undesirable, e.g., in acute iritis and in narrow-angle (angle-closure) glaucoma.

WARNINGS

Cardiovascular Disease:
Cevimeline can potentially alter cardiac conduction and/or heart rate. Patients with significant cardiovascular disease may potentially be unable to compensate for transient changes in hemodynamics or rhythm induced by EVOXAC®. EVOXAC® should be used with caution and under close medical supervision in patients with a history of cardiovascular disease evidenced by angina pectoris or myocardial infarction.

Pulmonary Disease:
Cevimeline can potentially increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. Cevimeline should be administered with caution and with close medical supervision to patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.

Ocular:
Ophthalmic formulations of muscarinic agonists have been reported to cause visual blurring which may result in decreased visual acuity, especially at night and in patients with central lens changes, and to cause impairment of depth perception. Caution should be advised while driving at night or performing hazardous activities in reduced lighting.

PRECAUTIONS

General:
Cevimeline toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include: headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal spasm, nausea, vomiting, diarrhea, atrioventricular block, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors.

Cevimeline should be administered with caution to patients with a history of nephrolithiasis or cholelithiasis. Contractions of the gallbladder or biliary smooth muscle could precipitate complications such as cholecystitis, cholangitis and biliary obstruction. An increase in the ureteral smooth muscle tone could theoretically precipitate renal colic or ureteral reflux in patients with nephrolithiasis.

Information for Patients: Patients should be informed that cevimeline may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient sweats excessively while taking cevimeline, dehydration may develop. The patient should drink extra water and consult a health care provider.

Drug Interactions:
Cevimeline should be administered with caution to patients taking beta adrenergic antagonists, because of the possibility of conduction disturbances. Drugs with parasympathomimetic effects administered concurrently with cevimeline can be expected to have additive effects. Cevimeline might interfere with desirable antimuscarinic effects of drugs used concomitantly.

> Drugs which inhibit CYP2D6 and CYP3A3/4 also inhibit the metabolism of cevimeline. Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events. In an *in vitro* study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited by exposure to cevimeline.
>
> ***Geriatric Use:***
> Although clinical studies of cevimeline included subjects over the age of 65, the numbers were not sufficient to determine whether they respond differently from younger subjects. Special care should be exercised when cevimeline treatment is initiated in an elderly patient, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in the elderly.

Finally, the PI explains that patients in clinical trials utilizing cevimeline in Sjögren's syndrome experienced adverse events associated with muscarinic agonism. The following adverse events associated with muscarinic agonism were observed (>10% incidence): Excessive Sweating (18.7%), Nausea (13.8%), Rhinitis (11.2%), and Diarrhea (10.3%).

De Facto Omission of Risk Information

The wall calendar and dry erase board present effectiveness claims for Evoxac but fail to communicate risk information associated with its use. Risk information for Evoxac is printed on the back of the wall calendar and dry erase board; however, as a practical matter, this information is not visible or even accessible to the viewer. The backs of the calendar and dry erase board are covered with an adhesive and completely obscured by an opaque paper backing to prevent sticking. This backing completely covers all the risk information presented. Furthermore, the wall calendar and dry erase board are designed to be adhered to walls or similar surfaces, so even once the opaque paper backing is removed, the pieces are not designed to allow the risk information to be visible or even accessible. Presenting risk information in this manner is not sufficient to ensure that the claims in each part of the wall calendar and dry erase board are truthful and non-misleading. As a result, the pieces misleadingly suggest that Evoxac is safer than has been demonstrated by substantial evidence or substantial clinical evidence. We note that, even if the information on the back of the calendar or dry erase board could be accessed (i.e., the materials did not adhere to the wall and could be flipped), the misbranding would not be cured. Your failure to include any risk information on the front of these materials cannot be corrected merely by including that information in another part of the materials. Rather, there must be some disclosure beyond a disclaimer in the same place in which the effectiveness claims appear. *Cf.*, 21 CFR 202.1(e)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, your wall calendar and dry erase board misbrand Evoxac in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) and 321(n).

DDMAC requests that Daiichi immediately cease the dissemination of violative promotional materials for Evoxac such as those described above. Please submit a written response to this letter on or before January 29, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Evoxac the same as or similar to 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, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to the MACMIS #14792 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 Evoxac 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., M.B.A.
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/

Mark Askine
1/12/2007 09:30:56 AM
for Thomas W. Abrams