DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Anthony J. Corrado, Director
Commercial Regulatory Affairs
Daiichi Sankyo, Inc.
Two Hilton Court
Parsipanny, NJ 07054

RE: NDA # 021286 & 021532
BENICAR® (olmesartan medoxomil) tablets, for oral use
BENICAR HCT® (olmesartan medoxomil - hydrochlorothiazide) Tablets
MA #527

Dear Mr. Corrado:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional Direct Mail - Wave 4 (Direct Mail)(DSBN12101324) for BENICAR® (olmesartan medoxomil) tablets, for oral use (Benicar) and BENICAR® HCT (olmesartan medoxomil - hydrochlorothiazide) Tablets (Benicar HCT) submitted by Daiichi Sankyo, Inc. (Daiichi Sankyo) under cover of Form FDA 2253. The promotional material is misleading because it makes unsubstantiated efficacy claims associated with Benicar and Benicar HCT. Therefore, the Direct Mail misbrands Benicar and Benicar HCT in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a). *Cf*. 21 CFR 202.1(e)(6)(i); (e)(7)(i).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Benicar and Benicar HCT.[1]

According to the FDA-Approved product labeling (PI)[2], Benicar is indicated for the treatment of hypertension, alone or with other antihypertensive agents. Benicar HCT is also indicated for the treatment of hypertension, but is not indicated for initial therapy.

Benicar and Benicar HCT are associated with a Boxed Warning regarding fetal toxicity and both drug products are contraindicated in diabetic patients who are on aliskiren therapy.

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.
[2] The versions of the Benicar PI and Benicar HCT PI that were approved when the piece cited in this letter was disseminated and the versions referred to in this letter are dated 11/2012. However, new versions were approved on 07/03/13.

Benicar HCT is also contraindicated in patients who have hypersensitivity to any of its components and in patients with anuria or in patients who have hypersensitivity to other sulfonamide-derived drugs.

Benicar and Benicar HCT are associated with warnings and precautions regarding hypotension in volume- or salt-depleted patients and impaired renal function. Benicar is also associated with a Warning and Precaution regarding morbidity in infants. Benicar HCT is associated with additional Warnings regarding hepatic impairment, hypersensitivity reaction, systemic lupus erythematous, lithium interaction, acute myopia and secondary angle-closure glaucoma. Benicar HCT's PI also includes a general precaution regarding electrolyte imbalances, hyperuricemia, effects in diabetic and post-sympathectomy patients, and increases in cholesterol and triglyceride levels. The most common adverse reaction associated with Benicar is dizziness. The most common adverse reactions associated with Benicar HCT are nausea, hyperuricemia, dizziness, and upper respiratory tract infection.

Unsubstantiated Efficacy Claims

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Direct Mail includes the following claims and presentations (emphasis in original):

- "Which hypertensive therapy helped 7 out of 10 challenging patients reach goal?"
- "In the BeniSYS trial, 70% of patients reached a BP goal of <140/90 mm Hg by week 12 (mean baseline BP: 171/95 mm Hg)."[3]
- "*In the BeniSYS trial*
  35 mm Hg mean SBP [systolic blood pressure] reduction in challenging patients titrated up to BENICAR HCT® 40/25 mg"[3]
- A bar graph depicting the change in mean SBP (mm Hg) from baseline:
  -17 for Benicar 20 mg, -18 for Benicar 40 mg, -30 for Benicar HCT 40/12.5 mg, and -35 for Benicar 40/25 mg[3]
- "7 out of 10 challenging patients reached goal with BENICAR and BENICAR HCT"
- "Over 70% to <140/90 mm Hg by week 12"[3]
  (Cumulative goal attainment: 70.4%). The cumulative goal attainment for BPs 140/90 mm Hg, <130/85 mm Hg, <120/80 mm Hg were secondary endpoints."[3,4]
- "26 patients (15.4%) achieved BP normalization of <120/80 mm Hg and exited the study and last observation was carried forward; these patients are included in the 70% who reached goal."[3]

The above claims and presentations are misleading because they imply that Benicar and Benicar HCT have demonstrated efficacy in "challenging patients" by helping them reduce high blood pressure and reach their goals based on the referenced study. The references cited describe the results of an open-label, uncontrolled trial, which due to lack of placebo control or blinding, does not provide substantial evidence or substantial clinical experience to

[3] Izzo JL Jr, Neutel JM, Silfani T, Dubiel R, Walker F. Efficacy and safety of treating stage 2 systolic hypertension with olmesartan and olmesartan/HCTZ: results of an open-label titration study. *J Clin Hypertens (Greenwich)*. 2007;9;36-44.
[4] Data on file. Daiichi Sankyo, Inc., Parsippany, NJ. (Study 443: BeniSYS Clinical Study Report)

support the efficacy claims and presentations above. Furthermore, the referenced study excluded such "challenging patients" as those with severe hypertension and uncontrolled blood pressure during the run-in phase of the study, and therefore did not properly evaluate this subgroup. Moreover, the bar graph depicting the change from baseline in mean SBP (mm Hg) portrays a level of blood pressure reduction greater than that seen in well-controlled pivotal trials described in the Benicar HCT PI. According to the Benicar HCT PI, the placebo-adjusted changes in sitting SBP in a placebo-controlled clinical trial comparing Benicar and Benicar HCT were as follows: 12mmHg for Benicar 20 mg, 13 mmHg for Benicar 40 mg, 16 mmHg for Benicar HCT 40/12.5 mg, and 24 mmHg for Benicar HCT 40/25 mg. Thus, the presentation of blood pressure reduction in "challenging patients" in the Direct Mail is not supported by substantial evidence or substantial clinical experience and is misleading.

Conclusion and Requested Action

For the reasons discussed above, the Direct Mail misbrands Benicar and Benicar HCT in violation of the FD&C Act, 21 U.S.C. 352(a). *Cf*. 21 CFR 202.1 (e)(6)(i); (e)(7)(i).

OPDP requests that Daiichi Sankyo immediately cease the dissemination of violative promotional materials for Benicar and Benicar HCT such as those described above. Please submit a written response to this letter on or before November 19, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Benicar and Benicar HCT that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA # 527 in addition to the NDA numbers in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds 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 Benicar and Benicar HCT comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Amy Toscano, Pharm.D., RAC, CPA
Team Leader
Office of Prescription Drug Promotion

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/s/

ZARNA PATEL
11/05/2013

AMY TOSCANO
11/05/2013