DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Joseph Pieroni
President/CEO
Sankyo Pharma Inc.
Two Hilton Court
Parsippany, NJ 07054

RE: NDA # 21-286 & 21-532
Benicar (olmesartan medoxomil) Tablets
Benicar HCT (olmesartan medoxomil/hydrochlorothiazide) Tablets
MACMIS ID 13421

WARNING LETTER

Dear Mr. Pieroni:

The Division of Drug Marketing, Advertising, and Communications (DDMAC), in consultation with the Division of Cardiovascular and Renal Products (DCaRP), has reviewed a sales aid (SPBN04-0149) for Benicar® (olmesartan medoxomil) Tablets and Benicar® HCT (olmesartan medoxomil and hydrochlorothiazide) Tablets submitted by Sankyo Pharma Development (Sankyo) under cover of Form FDA 2253. The sales aid is false or misleading because it contains unsubstantiated effectiveness and superiority claims, and omits and minimizes information on the risks associated with Benicar and Benicar HCT, and, therefore, misbrands the drugs in violation of section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 352(a). These claims and omissions raise significant public health and safety concerns because they suggest without adequate substantiation that Benicar and Benicar HCT are superior to other antihypertensive drug products and are safer and more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to the FDA-approved product labeling (PI), Benicar and Benicar HCT are angiotensin II receptor antagonists. Benicar is indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents. Benicar HCT, which is a fixed dose combination of olmesartan medoxomil and hydrochlorothiazide, is also indicated for the treatment of hypertension, but is not indicated for initial therapy. Both drug products are contraindicated in patients who are hypersensitive to any of their components. BENICAR HCT is also contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

The PI's for Benicar and Benicar HCT include the following Boxed Warning regarding use in pregnancy:

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Benicar®/Benicar HCT™ should be discontinued as soon as possible. **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

Additional information on the risks of using the drugs in pregnancy appears in the Warnings section of their respective PIs.

The PI for Benicar contains the following additional warning:

> **Hypotension in Volume- or Salt-Depleted Patients**
> In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with BENICAR®. Treatment should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline (See **DOSAGE AND ADMINISTRATION**). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

A virtually identical warning appears in the PI for Benicar HCT.

The PI for Benicar HCT also includes the following warnings regarding its hydrochlorothiazide component:

> **Fetal/Neonatal Morbidity and Mortality**: Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.
>
> **Hepatic Impairment**: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
>
> **Hypersensitivity Reaction**: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
>
> **Systemic Lupus Erythematosus**: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

> **Lithium Interaction**: Lithium generally should not be given with thiazides (see **PRECAUTIONS: Drug Interactions**; *Hydrochlorothiazide, Lithium).*

The PI's for Benicar and Benicar HCT contain the following precaution:

> In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Unsubstantiated Superiority Claims

Your sales aid contains numerous claims and presentations that suggest that Benicar and Benicar HCT are more effective than other angiotensin II receptor antagonists and their hydrochlorothiazide combination products. The references provided in support of these claims, as is further detailed in the examples provided below, do not constitute substantial evidence or substantial clinical experience to support these claims and representations. The studies did not generate valid data to support the product comparisons because, among other factors, the studies either (1) were open-label, uncontrolled trials; (2) were meta-analyses; (3) were titration-to-effect comparisons; or (4) did not compare drugs administered at their maximum approved dosages.

- Benicar vs. Diovan

A number of claims and presentations in the sales aid suggest that Benicar is superior to **Diovan (valsartan)**. For example, page four of the sales aid includes a graphic demonstrating the percentage of patients who obtained goal blood pressure after receiving Benicar or Diovan. These graphs suggest that Benicar is superior to Diovan by indicating that a significantly higher percentage of patients on Benicar attained the "aggressive goal" blood pressure of <130/85 mm Hg than did patients on Diovan.

FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Benicar is superior to Diovan. The reference cited in support of the claim on page four, for example, does not provide substantial evidence or substantial clinical experience because the patients enrolled in the Oparil study[1] did not receive the maximum labeled dose of Diovan; the study therefore cannot support the claim of superior effectiveness for Benicar. In comparing your drug with another product, it is important to choose an appropriate dose and dose regimen of both your drug and the comparator drug.[2] In examining the results of a comparison of two treatments, it is important to consider whether an apparently less effective treatment has been used at too low a dose. In general, a claim of superiority should be based on a comparison of the maximum dose of two drug products in two adequate, well designed, head-to-head clinical trials.

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[1] Oparil S, Williams D, Chrysant SG, et al. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. *J Clin Hypertens.* 2001;3:283-291.

[2] Guidance for Industry, "E 10 Choice of Control Group and Related Issues in Clinical Trials" dated May 2001("E10") at 8.

The references cited elsewhere in the sales aid to suggest that Benicar is superior to Diovan also fail to constitute substantial evidence or substantial clinical experience to support such a claim. For example, page five of the sales aid indicates that Benicar is more effective than both Diovan and Cozaar (losartan potassium), but the study referenced to support the claims on this page – Sankyo's Study[ ]which was submitted to the DCaRP on[ ]– did not demonstrate any statistically significant difference in blood pressure reductions at week twelve among Benicar (olmesartan medoxomil), Diovan (valsartan), and Cozaar (losartan potassium) when each was[ ]to maximum labeled dosages.

- Benicar vs. Norvasc

Your sales aid also includes a pull-out that contains a graphic of the percentage of patients who obtained a goal blood pressure of < 130/85 mm Hg while receiving Benicar versus **Norvasc (amlodipine)**, accompanied by the statement that "More BENICAR patients achieved aggressive BP [blood pressure] goals than patients on amlodipine." According to the graphic, the percentage of patients who obtained the "aggressive" systolic blood pressure goal of < 130 mm Hg as well as the "aggressive" diastolic blood pressure goal of < 85 mm Hg was significantly higher for Benicar than for Norvasc. However, the reference cited in support of this presentation, the Chrysant Study,[3] does not provide evidence of superiority, as this trial did not use the maximum labeled dose of Norvasc (i.e., 10 mg daily). In comparing your drug with another product, it is important to choose an appropriate dose and dose regimen of both your drug and the comparator drug – i.e., for a claim of superior effectiveness, the comparative trial should use the maximum dose of the comparator drug product in adequate, well designed, head-to-head clinical trials. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Benicar is superior to Norvasc.

- Benicar vs. Plendil

In addition to suggesting that Benicar is superior to Norvasc, the pull-out page also misleadingly suggests that Benicar is superior to **Plendil (felodipine)**. The claims and presentations discussed above are followed by the claim "A second study vs the CCB felodipine yielded similar results in mean blood pressure reductions." The reference provided for this claim, the Stumpe and Ludwig study,[4] does not constitute substantial evidence or substantial clinical experience in support of this claim because it showed similar blood pressure reductions for Benicar and Plendil, but no evidence of Benicar's superiority. FDA is not aware of substantial evidence or substantial clinical experience demonstrating Benicar is superior to Plendil.

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[3] Chrysant SG, Marbury TC, Robinson TD. Antihypertensive efficacy and safety of olmesartan medoxomil compared with amlodipine for mild-to-moderate hypertension. *J Hum Hypertens*. 2003;17:425-432.

[4] Stumpe KO, Ludwig M. Antihypertensive efficacy of olmesartan compared with other antihypertensive drugs. *J Hum Hypertens*. 2002;16(supp 12):S24-S28.

- Benicar vs. Cozaar, Diovan, and Avapro
- Benicar HCT vs. Hyzaar, Diovan HCT, and Avalide

In addition to the presentations discussed above, your sales aid also includes numerous claims and presentations that misleadingly suggest that Benicar and Benicar HCT are also superior to a number of other competitors. For example, the totality of the presentations on pages six, seven, and eight of the sales aid suggest that Benicar is more effective than **Cozaar (losartan)**, **Diovan (valsartan)**, and **Avapro (irbesartan)**. These presentations also suggest that Benicar HCT is superior to **Hyzaar (losartan and hydrochlorothiazide)**, **Diovan HCT (valsartan and hydrochlorothiazide)**, and **Avalide (irbesartan and hydrochlorothiazide)**.

Specifically, the sales aid presents the systolic and diastolic blood pressure reductions associated with use of Benicar at the maximum labeled dose directly across from a graphic demonstrating the diastolic blood pressure reductions observed in patients who received the starting doses of Cozaar, Hyzaar, Diovan, Diovan HCT, Avapro, and Avalide. This presentation is immediately followed by the presentation of systolic and diastolic blood pressure reductions observed in patients who received Benicar HCT at maximum doses. The data presented in the graphics on these pages, as well as the claims accompanying these presentations, suggest that Benicar and Benicar HCT are more effective than the other angiotensin II receptor antagonists and their hydrochlorothiazide combination products. The references cited for these presentations, however, do not constitute substantial evidence or substantial clinical experience in support of these claims of superiority. For example, the reference cited for the data for the competitor drugs presented on page seven of the sales aid, Conlin et al.,[5] reflects the results of a pooled meta-analysis of forty-three double-blind, randomized, controlled trials in which the patients received only the starting doses of these drugs, not their maximum doses. In addition, the comparisons across these studies are misleading since they were not concurrently controlled studies. Meta-analyses are historically (or externally) controlled trials and can be biased because the results are known before the comparison is made. Moreover, different patient populations can differ greatly in their responses to a given drug or drug class. In order to support a claim of superiority to other drug products, data from head-to-head clinical studies using the maximum approved doses of the comparator drug would be needed. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Benicar and Benicar HCT are more effective than these other angiotensin II receptor antagonists and their hydrochlorothiazide combination products. Thus, these claims and presentations are misleading.

[5] Conlin PR, Spence JD, Williams B, et al. Angiotensin II antagonists for hypertension: are there differences in efficacy? *Am J Hypertens.* 2000;13(4 Pt 1):457-459.

Unsubstantiated Effectiveness Claim

The sales aid contains the following efficacy claims:

- "Nearly 7 out of 10 patients on BENICAR or BENICAR HCT reached the aggressive goal of ≤ 130/85 mm Hg and more than half of these patients did so on BENICAR monotherapy"
- "69% to goal"
- "Majority of patients reached goal of ≤ 130/85 mm Hg on BENICAR or BENICAR HCT"
- "Stage 1 patients reached goal 89%"
- "Stage 2 patients reached goal 54%"
- "In a clinical trial, BENICAR and BENICAR HCT helped a majority of patients reach aggressive goals" (original emphasis)
- "In a clinical trial, More patients on BENICAR and BENICAR HCT reached aggressive goals" (original emphasis)
- "69% of patients on BENICAR or titrated up to the maximum dose of BENICAR HCT reached the aggressive goal of ≤ 130/85 mm Hg
  - 89% of Stage 1 patients reached goal
  - 54% of Stage 2 patients reached goal"

The reference cited in support of these claims, the Neutel study,[6] does not provide substantial evidence or substantial clinical experience to support these claims, as it was an open-label, uncontrolled (or "baseline-controlled") trial, without a concurrent placebo control. The level of blood pressure reduction reported in this study for Benicar and Benicar HCT is far greater than that seen in well-controlled trials. In fact, the recent study submitted by Sankyo showed that only 27.3% of the patients administered 40 mg Benicar once daily (the maximum dose) achieved a BP of <130 mm/85 mm Hg. This controlled study would plainly not support claims that the majority of patients on Benicar reached goal BP (i.e., < 130/85 mm Hg). Thus, these claims are misleading because they overstate the efficacy for Benicar and Benicar HCT on the basis of an inadequate study.

Additionally, the sales aid contains the following claims regarding "goal attainment:"

- "Nearly 7 out of 10 patients on BENICAR or BENICAR HCT reached the aggressive goal of ≤ 130/85 mm Hg and more than half of these patients did so on BENICAR monotherapy"
- "73% reached the aggressive SBP goal of ≤ 130 mm Hg"
- "87% reached the aggressive DBP goal of ≤ 85 mm Hg"
- "More than half the patients who reached the aggressive goal of ≤ 130/85 mm Hg on BENICAR or BENICAR HCT were controlled on BENICAR monotherapy"
- "Other trials demonstrate excellent monotherapy goal attainment vs other antihypertensives"

[6] Neutel JM, Smith DHG, Weber MA, et al. Use of an olmesartan medoxomil-based treatment algorithm for hypertension control. *J Clin Hypertens.* 2004;6:168-174.

The "data on file" cited as support for these claims come from a secondary analysis of the same study published in 2004 by Neutel et al. As noted above, the Neutel study does not constitute substantial evidence or substantial clinical experience because it was an open-label, uncontrolled trial.

Furthermore, the reference to the NHANES data (which states that only 31% of patients with hypertension are controlled) on page two of the sales aid supports the suggestion that Benicar or Benicar HCT will improve control rates. Even if the Neutel data were not limited as described above, there is still no way to validly compare results of clinial trails (such as Neutel) with results from community experience (such as NHANES). The suggestion that physicians using Benicar or Benicar HCT in practice will see improved control rates is therefore misleading.

Page eleven of the sales aid presents data obtained from the Hypertension Optimal Treatment (HOT) trial with the claim "Lower diastolic blood pressure associated with fewer MIs." This presentation is framed by the efficacy claims "Reaching aggressive BP goals with BENICAR" and "GREAT BP REDUCTIONS FOR MORE AGGRESSIVE GOALS." When these myocardial infarction (MI) claims are considered in combination with the numerous claims throughout the sales aid (including on the page of the sales aid that faces this presentation) promoting Benicar's ability to lower diastolic blood pressure, the inescapable suggestion is that treatment with Benicar has been shown to decrease the chance of a patient having an MI. This claim is false or misleading. Benicar was not included in the HOT trial itself, and FDA is not aware of substantial evidence or substantial clinical experience that would support a claim that Benicar may lower the risk of a patient having an MI.

Omission and Minimization of Risk Information

The sales aid also fails to include risk information necessary to qualify the numerous safety and effectiveness claims presented for Benicar and Benicar HCT throughout the thirteen pages of the aid. Other than the Boxed Warning information regarding the use Benicar and Benicar HCT during pregnancy, which is presented on page two of the sales aid, and the statement "Please see boxed **WARNING regarding use in Pregnancy** in the prescribing information for BENICAR and BENICAR HCT," which is presented at the bottom of various pages of the sales aid, the only additional information included in the sales aid regarding the risks associated with the use of Benicar and Benicar HCT is found on page eleven under the header "**The great efficacy of BENICAR and BENICAR HCT—combined with favorable safety and tolerability**" (emphasis in original).

The section under this header discloses information on the most common adverse events occurring with Benicar and Benicar HCT, but omits serious risk information from the PI regarding the use of Benicar and Benicar HCT in pregnancy, in patients with an activated renin-angiotensin system, and in patients with unilateral or bilateral renal artery stenosis. With respect to the pregnancy warnings, we acknowledge the sales aid displays and references the black box warning. However, it fails to disclose any of the other serious pregnancy-related risk information included in the PI and set forth on page two of this letter. With respect to the renal artery stenosis precaution, the sales aid also fails to disclose any of the serious risk information

included in the PI and set forth on page three of this letter. Additionally, the sales aid fails to disclose risk information regarding the use of Benicar HCT in patients with impaired hepatic function or systemic lupus erythematosus and lithium interactions.

In addition to omitting important risks from the PI, the sales aid also minimizes the risks it does present. The risks that are presented on page eleven are preceded by the large, bold-faced header described above, which reads: "The great efficacy of BENICAR and BENICAR HCT—combined with favorable safety and tolerability." The use of this prominent header to frame the presentation of risk information significantly minimizes the serious risks that are associated with both Benicar and Benicar HCT, and misleadingly signals to the reader that the risks that are presented on this page are minimal in nature.

Conclusion and Requested Action

The sales aid contains unsubstantiated effectiveness and superiority claims and omits information on the risks associated with Benicar and Benicar HCT, and, therefore, misbrands the drugs in violation of section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 352(a).

DDMAC requests that Sankyo immediately cease the dissemination of promotional materials for Benicar or Benicar HCT the same as or similar to those described above. To that end, we note there are similar claims and presentations for Benicar and Benicar HCT in several other promotional materials submitted under cover of Form FDA 2253, including both the Benicar.com website and a Slim Jim (SPBN04-0192) that was recently disseminated at the 2005 American Society of Hypertension Conference in San Francisco, California. Please submit a written response to this letter on or before January 23, 2006, describing your intent to comply with this request, listing all promotional materials for Benicar or Benicar HCT 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, or facsimile at (301) 796-9878. In all future correspondence regarding this matter, please refer to MACMIS 13421 in addition to the NDA numbers. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

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 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, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams
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