DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

November 21, 1997

TRANSMITTED VIA FACSIMILE

Richard U. De Schutter
Chairman, President and CEO
G.D. Searle & Co.
5200 Old Orchard Road
Skokie, IL 60077

Re: Covera-HS (verapamil hydrochloride)
Extended Release Tablets Controlled-Onset
NDA No. 20-552
MACMIS No. 5905

WARNING LETTER

Dear Mr. De Schutter:

This Warning Letter addresses G.D. Searle & Co. ("Searle's") dissemination of a radio broadcast advertisement for Covera-HS (verapamil hydrochloride) Extended Release Tablets Controlled-Onset. This advertisement was broadcast in Spanish by several radio stations located in the Commonwealth of Puerto Rico during May and June, 1997. The Division of Drug Marketing, Advertising, and Communications ("DDMAC") has reviewed this advertisement as part of its monitoring and surveillance program. DDMAC has concluded that Searle's radio advertisement is misleading and lacking in fair balance in violation of the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U. S. C. §§ 352(n) and 321(n), and applicable regulations. By its dissemination of this advertisement, Searle is misbranding Covera-HS.

Under Section 502(n) of the Act (21 U.S.C. § 502(n)), all prescription drug advertisements must contain a true statement of information in brief summary relating to side effects, contraindications, and effectiveness, as shall be required in FDA regulations. The prescription drug regulations at 21 CFR § 202.1(e)(1) provide that radio broadcast advertisements shall include information relating to the major side effects and contraindications of the advertised drugs in the audio presentation, and, unless adequate provision is made for dissemination of the approved labeling in connection with the broadcast, a brief summary of all necessary information related to side effects and contraindications. DDMAC concludes from its review of Searle's advertisement that Searle failed to provide such disclosures (information relating to the major side effects and contraindications, and dissemination of the approved labeling or

a brief summary of information related to side effects and contraindications) in conjunction with the broadcasts.

The prescription drug advertising regulations also provide that an advertisement is false, lacking in fair balance or otherwise misleading if it contains a representation or suggestion, not approved in the labeling that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience (21 CFR § 202.1(e)(6)(1)). Searle's claim in the radio advertisement suggests that Covera-HS provides special benefits to protect hypertensive patients during the morning hours of increased risk has not been demonstrated by substantial evidence or substantial clinical experience.

Furthermore, Searle failed to submit its radio advertisement to FDA as required by the post-marketing reporting requirements (21 CFR §314.81(b)(3)(i)).

Failure to Disclose Major Side Effects and Contraindications

As described above, in all prescription drug broadcast advertisements, sponsors are required to disclose information relating to the major side effects and contraindications of the advertised drug. This is important information for consumers and healthcare providers because the use of Covera-HS is contraindicated in patients with a variety of cardiac conditions. In addition, the use of Covera-HS is associated with adverse events including, but not limited to, first-degree AV block, hepatocellular injury, bradycardia, constipation, headache, dizziness, fatigue, and edema. There are also significant interactions between verapamil products such as Covera-HS and other medications such as beta-blockers that require caution and close monitoring or adjusting doses of verapamil or other medications. Some of these risks are associated with the effects of the drug, some with the patient's clinical status, and some with interactions between Covera-HS and concomitant drug therapies. Because Searle's radio broadcast advertisement failed to provide such disclosures, it lacks fair balance and is, therefore, misleading.

Failure to Provide a Brief Summary or Make Adequate Provision for Dissemination of the Approved Product Labeling

The regulations specifically require that all broadcast advertisements for prescription drugs contain a brief summary of all necessary information related to side effects and contraindications[1] or make adequate provision for dissemination of the approved product labeling (21 CFR 202.1(e)(1)). Searle's advertisement is misleading and lacking in fair balance in that it fails to present a brief summary or make adequate provision for dissemination of the product labeling.

Unsupported Effectiveness Claim

Searle's radio advertisement presents claims concerning the release of Covera-HS in relation to the risks of hypertension. The advertisement states or suggests that there is increased risk from hypertension in the morning hours and that a new medicine, Covera-HS, provides benefits to protect the patient during these morning hours. The advertisement also suggests that Covera-HS is superior to other antihypertensive agents because of its release of the drug during the hours of increased risk.

Although the approved product labeling describes Covera-HS as a "unique delivery system, designed for bedtime dosing," Searle has not presented adequate evidence to substantiate its claim that this delivery system offers clinical benefits that differ from that obtained with other antihypertensive therapies. Searle has not demonstrated that Covera-HS provides any greater benefit than any other verapamil product or other antihypertensive agent. These claims are unsupported and therefore misleading.

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1 The information relating to "side effects and contraindications" shall include side effects, warnings, precautions, and contraindications, and any such information under such headings as cautions, special considerations, important notes, etc. 21 CFR § 202.1(e)(3)(iii).

Failure to Submit Post-marketing Reports

Finally, although this advertisement was disseminated by three radio stations over a two month period of time, Searle failed to submit the radio broadcast advertisement to FDA. Such submissions are required at the time of its first use under the post-marketing reporting requirements. (21 CFR 314.81(b)(3)(i)).

Conclusions and Requested Actions

It is our understanding that this advertisement has been discontinued in Puerto Rico. However, DDMAC has concluded that Searle's activities resulted in the dissemination of misleading and incomplete information about Covera-HS. Accordingly, Searle should assure FDA that similar advertisements are not being disseminated anywhere in the United States or its territories and possessions. In addition, Searle should propose an action plan to disseminate accurate and complete information to the audience that received the misleading message. We invite you to meet with us in the near future to discuss our concerns and possible remedies to correct the misleading information disseminated in this radio advertising campaign.

Searle's action plan should be submitted to DDMAC for approval. The action plan should be implemented as soon as possible after such approval.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of Searle's promotional campaign for Covera-HS and we may determine that additional remedial measures may be necessary to fully correct the misleading messages resulting from Searle's violative conduct. Searle's response should be received no later than December 5, 1997. If Searle has any questions or comments, please contact Janet Norden, Thomas Abrams, or Norman A. Drezin, Esq. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Searle that only written communications are considered official.

Richard U. De Schutter
G.D. Searle & Co.
Covera-HS (verapamil hydrochloride)
Extended-Release Tablets
NDA No. 20-552

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 5905.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

Minnie Baylor-Henry, R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising, and Communications