DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-552/S-002

G.D. Searle LLC
Attention: Ms. Tina Shelbourn
4901 Searle Parkway
Skokie, IL 60077

Dear Ms. Shelbourn:

Please refer to your supplemental new drug application dated November 4, 1999 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Covera-HS (verapamil hydrochloride) 180 and 240 mg Tablets.

We acknowledge receipt of your submission dated October 26, 2001 that constituted a complete response to our July 27, 2000 approvable letter.

This supplemental new drug application provides for final printed labeling revised as follows:

CLINICAL PHARMACOLOGY

- The following text in the **CLINICAL PHARMACOLOGY** section has been deleted:

  In general, bioavailability of Covera-HS is higher and half-life longer in older (>65 yrs) subjects. Lean body weight also affects its pharmacokinetics inversely, but no gender difference was observed in the clinical trials of Covera-HS. However, there are conflicting data in literature suggesting that verapamil clearance decreased with age in women to a greater degree than in men.

- A **Geriatric Use** subsection has been added to the **CLINICAL PHARMACOLOGY** section as follows:

  Geriatric Use: The pharmacokinetics of Covera-HS were studied after 5 consecutive nights of dosing 180 mg in 30 healthy young (19-43 years) versus 30 healthy elderly (65-80 years) male and female subjects. Older subjects had significantly higher mean verapamil C_{max}, C_{min}, and $AUC_{(0\text{-}24h)}$ compared to younger subjects. Lean body mass was inversely related to AUC, but no gender difference was observed in the clinical trials of Covera-HS.

- The first sentence of the third paragraph of the **PRECAUTIONS/ General/ Use in patients with attenuated (decreased) neuromuscular transmission** section has been revised to read:

  It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, prolongs recovery from neuromuscular blocking agent vecuronium, and causes a worsening of myasthenia gravis.

- The following subsections have been added to the **Drug Interactions** section:

  Cytochrome inducers/inhibitors: In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450, CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Clinically significant interactions have been reported with inhibitors of CYP3A4 (e.g., erythromycin, ritonavir) causing elevation of plasma levels of verapamil while inducers of CYP3A4 (e.g., rifampin) have caused a lowering of plasma levels of verapamil; therefore, patients should be monitored for drug interactions.

  Aspirin: In a few reported cases, coadministration of verapamil with aspirin has led to increased bleeding times greater than observed with aspirin alone.

  Grapefruit juice: The intake of grapefruit juice may increase drug levels of verapamil.

- The **PRECAUTIONS/Elderly Use** section has been changed to **PRECAUTIONS/Geriatric Use** and revised as follows:

  Geriatric Use: Clinical studies of Covera-HS did not include sufficient numbers of subjects aged under 65 to determine whether they responded differently from older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

- Under the **ADVERSE REACTIONS** section, "extrapyramidal symptoms" has been added to the list of reactions in the *Nervous system* subsection.

In addition, minor editorial changes were noted. At the time of your next printing please make the following changes:

1. Under **CLINICAL PHARMACOLOGY,** change the **Geriatric use** subsection to read as follows:

   Geriatric use: The pharmacokinetics of Covera-HS were studied after 5 consecutive nights of dosing 180 mg in 30 healthy young (19-43 years) versus 30 healthy elderly (65-80 years) male and female subjects. Older subjects had significantly higher mean verapamil C_{max}, C_{min}, and $AUC_{(0\text{-}24h)}$ compared to younger subjects. These results were typical of the age-related differences seen with many drug products in clinical medicine. Older subjects had mean AUCs that were approximately 1.7-2.0 times higher than those of younger subjects as well as a longer average verapamil t_{12} (approximately 20 hr vs 13 hr). Lean body mass was inversely related to AUC, but no gender difference was observed in the clinical trials of Covera-HS. However, there are conflicting data in the literature suggesting that verapamil clearance may decrease with age in women to a greater degree than in men. Mean T_{max} was similar in young and elderly subjects.

2. Under **PRECAUTIONS,** change the **Drug interactions** subsection to read as follows:

   Drug-Drug interactions
   Drug interactions: Effects of other drugs on verapamil pharmacokinetics: In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, and CYP2C. Clinically significant interactions have been reported with inhibitors of CYP3A4 (eg, erythromycin, ritonavir) causing elevation of plasma levels of verapamil while inducers of CYP3A4 (eg, rifampin) have caused a lowering of plasma levels of verapamil (see Precautions: inducers/inhibitors).

3. Under **PRECAUTIONS/Drug Interactions**, change the **Grapefruit juice** subsection to read:

   Grapefruit juice: Grapefruit juice may significantly increase concentrations of verapamil. Grapefruit juice given to nine healthy volunteers increased S- and R- verapamil AUC_{0-12} by 36% and 28%, respectively. Steady state Cmax and Cmin of S-verapamil increased by 57% and 16.7%, respectively with grapefruit juice compared to control. Similarly, C_{max} and C_{min} of R-verapamil increased by 40% and 13%, respectively. Grapefruit juice did not affect half-life, nor was there a significant change in AUC_{0-12} ratio R/S compared to control. Grapefruit juice did not cause a significant difference in the PK of norverapamil. This increase in verapamil plasma concentration is not expected to have any clinical consequences.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your October 26, 2001 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton

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