DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED BY FACSIMILE**

Robert B. Clark
Vice President, US Regulatory
Pfizer Inc.
235 East 42nd Street
New York, New York 10017

**RE: NDA # 20-552**
**Covera-HS® (verapamil hydrochloride)**
**Extended-Release Tablets Controlled-Onset**
**MACMIS ID # 11163**

Dear Mr. Clark:

This letter concerns the dissemination of promotional materials for Covera®-HS (verapamil hydrochloride) Extended-Release Tablets Controlled-Onset. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a sales aid (UX0024620) for Covera-HS, submitted under cover of Form FDA 2253 by Pharmacia & Upjohn Company. DDMAC has determined that this sales aid contains an unsubstantiated superiority claim with respect to enalapril as well as several other unsubstantiated claims. In addition, your sales aid omits and minimizes risks associated with Covera-HS. Accordingly, the sales aid misleadingly overstates the efficacy of Covera-HS and minimizes its risks in violation of the Federal Food, Drug, and Cosmetic Act and FDA implementing regulations. 21 U.S.C. §§ 321(n) & 352(a). Cf. 21 CFR 202.1(e)(6)(i) & (ii).

**Background**

According to the approved product labeling (PI), "Covera-HS is indicated for the management of hypertension and angina." The drug is contraindicated in the following cardiovascular conditions: severe left ventricular dysfunction; hypotension (systolic pressure less than 90 mm HG) or cardiogenic shock; sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker); second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker); and patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). As stated in the PI, there have been reports of excessive bradycardia and AV block, including complete heart block, when the combination of beta-adrenergic blockers and sustained-release verapamil has been used for the treatment of hypertension. Moreover, although clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted, chronic verapamil treatment can increase serum digoxin levels by 50% to

75% during the first week of therapy, and this can result in digitalis toxicity, which may include both ventricular rates below 50/min at rest and asymptomatic hypotension. Covera-HS also interacts with other medications, including disopyramide, quinidine, lithium, carbamazepine, and theophylline, as described in greater detail in the Drug-Drug Interactions section of the PI.

Verapamil presents particular risks for patients with hepatic impairment. According to the Precautions section of the PI, "Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate-release verapamil to about 14 to 16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see Overdosage) should be carried out."

**Unsubstantiated Superiority Claim**

Your sales aid includes the claim, "In management of the hypertensive diabetic patient – When you need to go lower – Go with Covera-HS," along with a graph entitled, "Covera-HS effectively blunts morning BP surge, while an ACE inhibitor, enalapril, exerts its peak effects in the afternoon." The graph compares the peak blood pressure effect for Covera-HS taken at bedtime, a regimen that provides a peak effect in the morning, with enalapril taken in the morning, a regimen that provides a peak effect in the morning or afternoon. This combination of text and graphics suggests that Covera-HS is superior to enalapril because Covera-HS has its peak effect in the morning.

This claim is misleading. The data you present are based on a single trial that, among other design flaws, did not use the maximum labeled dose of enalapril. We are not aware of other data constituting substantial evidence or substantial clinical experience to support this claim.

**Other Unsubstantiated Claims**

Your sales aid includes a bar graph entitled, "Covera-HS – a non-dihydropyridine CCB – added to an ACE inhibitor may reduce proteinuria in diabetics more than an ACE inhibitor alone." This bar graph presents data for the "% change in albuminuria from baseline at 1 year" and describes changes of –55% and –68% for lisinopril (n=8) and sustained-release verapamil in combination with lisinopril (n=8), respectively, with a $p<.05$ for the combination versus lisinopril. The combination of text and graphics suggests that the combination of Covera-HS and lisinopril is useful in diabetes (i.e., it will reduce proteinuria in hypertensive, non-insulin-dependent diabetic patients with renal insufficiency).

This claim is misleading. The study cited in the sales aid, among other design flaws, included 16 patients, too few to support a conclusion that Covera-HS has any particular effect in patients with diabetes. Moreover, even if the study were adequately designed to substantiate the claimed effect in diabetes, there is no evidence that this small difference in proteinuria is of any clinical benefit to diabetic patients. We are not aware of any other data that would provide substantial evidence or substantial clinical experience to support the claim.

Your sales aid also recommends use of Covera-HS "In management of the hypertensive diabetic patient," and includes a graph entitled, "Covera-HS provides significant 24-hour BP reductions in diabetics and non-diabetics." The graph presents pooled data from three trials for blood pressure "[c]hange from baseline" for diabetics (n=23) and non-diabetics (n=250). The combination of text and graphics suggests some special benefit of Covera-HS in diabetics.

This claim is misleading. The data cited in the sales aid are not sufficient to substantiate the claimed effect in diabetic patients, because (among other reasons) they came from 23 patients, too few to support a conclusion that Covera-HS has any particular effect in patients with diabetes. We are not aware of any other data that would provide substantial evidence or substantial clinical experience to support the claim.

**Omission and Minimization of Risk Information**

Your sales aid recommends Covera-HS for "24-hour cardiovascular care," but omits information regarding the cardiovascular risks of treatment with Covera-HS. As noted above, the combined use of Covera-HS and beta-blockers may lead to excessive bradycardia and AV block, including complete heart block; combined use with digitalis may lead to digitalis toxicity; and there are potentially serious drug interactions with disopyramide, quinidine, lithium, carbamazapine, and theophylline.

Your sales aid also minimizes the risks of Covera-HS for patients with hepatic impairment. It states, in small, thin type at the bottom, "patients with impaired hepatic or renal function may be particularly sensitive to the effects of verapamil and should be monitored closely." This statement minimizes the risk of using Covera-HS in patients with hepatic impairment. It fails to convey that in addition to close monitoring, patients with severe hepatic dysfunction may require as much as a 70% reduction in dose, as stated in the PI. This information is essential for administering verapamil appropriately to this group of patients.

**Conclusion and Requested Action**

The sales aid claims that Covera-HS is superior to enalapril when, to our knowledge, this has not been demonstrated by substantial evidence or substantial clinical experience. Moreover, the sales aid contains claims regarding the clinical utility of Covera-HS in diabetic patients when, so far as we know, effectiveness specifically in diabetes has not been established by substantial evidence or substantial clinical experience. Finally, the sales aid fails to adequately present cardiovascular risk information relating to use of Covera-HS and fails to adequately present risk information relating to use of Covera-HS in patients with hepatic impairment. For these reasons, the sales aid is false or misleading and misbrands Covera-HS.

DDMAC requests that Pfizer immediately cease the dissemination of this sales aid and of any other promotional materials for Covera-HS that contain claims the same as or similar to those described above. Please submit a written response to this letter on or before November 7, 2003, describing your intent to comply with this request, listing all promotional materials for Covera-HS that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile 301-594-6771. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID # 11163 in addition to the NDA number.

Sincerely,

*{See appended electronic signature page}*

Andrew S.T. Haffer, Pharm.D.
Regulatory Review Officer
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
10/24/03 01:33:41 PM
Signed for Andrew S.T. Haffer, Pharm.D.

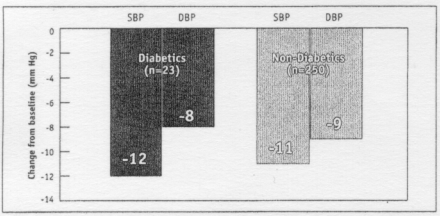
*In management of*
*the hypertensive diabetic patient*

# WHEN YOU NEED TO GO LOWER

*In management of the hypertensive diabetic patient*

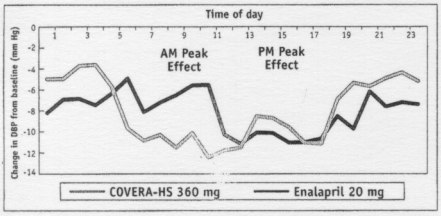
# GO WITH COVERA-HS

## COVERA-HS provides significant 24-hour BP reductions in diabetics and non-diabetics[1]




Pooled data from 3 randomized, double-blind, placebo-controlled studies in patients with hypertension (N=273). After a 2- to 4-week placebo lead-in period, patients were treated for 4 to 8 weeks with placebo or COVERA-HS. All values were significant at $P<.001$ compared with placebo.

## COVERA-HS effectively blunts morning BP surge, while an ACE inhibitor, enalapril, exerts its peak effects in the afternoon[1]




Results of an 8-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group study of patients with hypertension (N=357). Ambulatory blood pressure monitoring (ABPM) measurements were taken during the 4-hour interval after awakening. Mean 24-hour ABPM measurements were generally not different between active treatment groups. Agents were dosed according to prescribing information.

The clinical significance of reducing the early morning rise in blood pressure has not been established.

Contraindicated in patients with severe left ventricular dysfunction, hypotension, sick sinus syndrome, 2° or 3° AV block, or atrial flutter or fibrillation and an accessory bypass tract

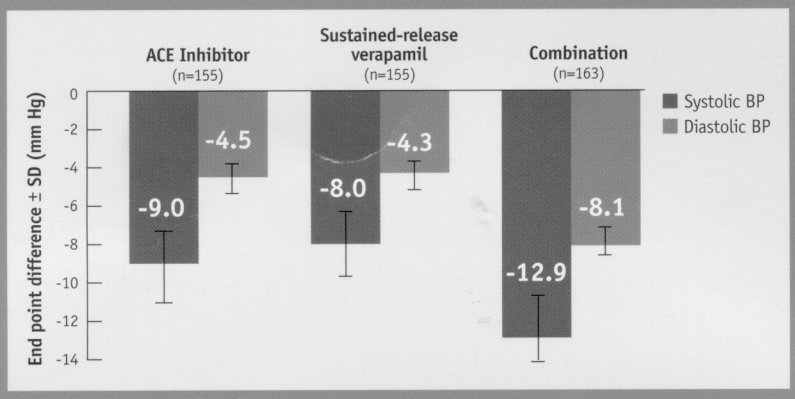
Concomitant therapy with oral antihypertensive agents, including ACE inhibitors, will usually have an additive effect on lowering BP; patients receiving these combinations should be appropriately monitored

Controlled Onset
COVERA-HS®
(verapamil HCl)
Extended-Release
180mg and 240mg Tablets

24-hour cardiovascular care

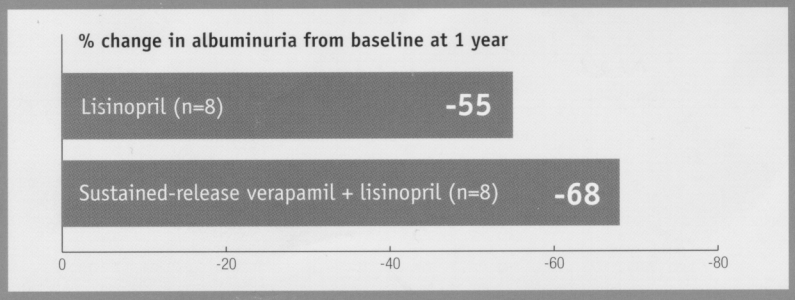
**Please see attached full prescribing information**

## Combination of a sustained-release form of verapamil and an ACE inhibitor significantly lowered BP more than either agent alone ($P<.01$)[2]




Results of a randomized, parallel, placebo-controlled, multicenter study of 631 patients (diabetic and non-diabetic) with stages I and II hypertension. After a 4-week single-blind placebo phase, patients received one of the following daily morning dosages in a double-blind fashion for 6 weeks: placebo, trandolapril 4 mg, sustained-release verapamil 240 mg, or trandolapril 4 mg/sustained-release verapamil 240 mg.

## COVERA-HS—a non-dihydropyridine CCB—added to an ACE inhibitor may reduce proteinuria in diabetics more than an ACE inhibitor alone[3,4]




Results of a 1-year, controlled, randomized study of hypertensive, non–insulin-dependent diabetic patients with renal insufficiency (N=30). $P<.05$ combination vs lisinopril.[4]

## Dihydropyridine CCBs (eg, amlodipine) do not reduce proteinuria[5-8]

## The most commonly reported side effects of COVERA-HS compared with placebo were constipation (11.7%/2.7%) and upper respiratory infection (5.4%/4.6%)

- **Low incidence of constipation of only 7.2% at 240 mg/day[9]**

## COVERA-HS is conveniently dosed once daily at bedtime up to 480 mg, and is available in 180 mg and 240 mg tablets

Patients with impaired hepatic or renal function may be particularly sensitive to the effects of verapamil and should be monitored closely.

**References: 1.** Data on file, Pharmacia Corporation. **2.** Messerli F, Frishman WH, Elliott WJ. Effects of verapamil and trandolapril in the treatment of hypertension. *Am J Hypertens.* 1998;11:322-327. **3.** Bakris GL, Weir MR, DeQuattro V, McMahon FG. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int.* 1998;54:1283-1289. **4.** Bakris GL, Barnhill BW, Sadler R. Treatment of arterial hypertension in diabetic humans: importance of therapeutic selection. *Kidney Int.* 1992;41:912-919. **5.** Abbott K, Smith A, Bakris GL. Effects of dihydropyridine calcium antagonists on albuminuria in patients with diabetes. *J Clin Pharmacol.* 1996;36:274-279. **6.** Bakris GL, Williams B. Angiotensin converting enzyme inhibitors and calcium antagonists alone or combined: does the progression of diabetic renal disease differ? *J Hypertens.* 1995;13(suppl 2):S95-S101. **7.** Bakris GL, Griffin KA, Picken MM, Bidani AK. Combined effects of an angiotensin converting enzyme inhibitor and a calcium antagonist on renal injury. *J Hypertens.* 1997;15:1181-1185. **8.** Smith AC, Toto R, Bakris GL. Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy. *Kidney Int.* 1998;54:889-896. **9.** Complete prescribing information for COVERA-HS (verapamil HCl).

Controlled Onset

COVERA-HS®
(verapamil HCl)

Extended-Release
180mg and 240mg Tablets

24-hour cardiovascular care

**Please see attached full prescribing information**

8452-09



PHARMACIA

UX0024620

March 2002