



NDA 20943/S-021

SUPPLEMENT APPROVAL

Elan Drug Delivery, Inc.
Attention: Carl Bauman, R.Ph.
Director, Product Safety and Labeling
1300 Gould Drive
Gainesville, GA 30504

Dear Mr. Bauman:

Please refer to your supplemental new drug application dated December 21, 2006, received December 21, 2006, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Verelan PM (verapamil hydrochloride) 100 mg, 200 mg, and 300 mg Extended-Release Capsules

We acknowledge receipt of your submissions dated July 27, 2007 and March 24 and December 1, 2009.

Your submission of December 1, 2009, constituted a complete response to our June 28, 2007, action letter.

This "Prior Approval" supplemental new drug application provides for conversion to the Physician Labeling Format and changes to the **HIGHLIGHTS, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, OVERDOASAGE, CLINICAL PHARMACOLOGY** and **PATIENT COUNSELING** sections of the label. The following changes were made:

1. The labeling has been converted to Physician Labeling Rule format.
2. In **HIGHLIGHTS/ADVERSE REACTIONS**, the contact name and number has been changed from:

Schwarz Pharma at 1-800-558-5114

To:

UCB, Inc. at 1-800-477-7877

3. In **DOSAGE AND ADMINISTRATION/Essential Hypertension**, the term "small patients" has been replaced with "low-weight patients."
4. In **DOSAGE AND ADMINISTRATION/Essential Hypertension**, the sentence "As with immediate-release and sustained-release verapamil, dosages of Verelan PM Capsules should be individualized and titration may be needed in some patients" has been deleted.

5. In **DOSAGE AND ADMINISTRATION/Essential Hypertension**, passive voice has been converted to active voice. The first paragraph now reads:

Administer Verelan PM once daily at bedtime. Clinical trials studied doses of 100 mg, 200 mg, 300 mg, and 400 mg. The usual daily dose of extended-release Verelan PM in clinical trials has been 200 mg given by mouth once daily at bedtime. In rare instances, initial doses of 100 mg a day may be warranted in patients who have an increased response to verapamil, e.g., patients with impaired renal function, impaired hepatic function, elderly, low-weight patients, etc. [*see Use in Specific Populations (8.5, 8.6, 8.7)*]. Base upward titration on therapeutic efficacy and safety evaluated approximately 24 hours after dosing. The antihypertensive effects of Verelan PM are evident within the first week of therapy.

6. In **DOSAGE AND ADMINISTRATION/Sprinkling the Capsule contents on Food**, passive voice had been converted to active voice. The first paragraph now reads:

Verelan PM Capsules may also be administered by carefully opening the capsule and sprinkling the pellets onto one tablespoonful of applesauce. Swallow the applesauce immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot, and it should be soft enough to be swallowed without chewing. Use any pellet/applesauce mixture immediately and do not store for future use. Absorption of the pellets sprinkled onto other foods has not been tested. This method of administration may be beneficial for patients who have difficulty swallowing whole capsules. Subdividing the contents of a Verelan PM capsule is not recommended

7. In **CONTRAINDICATIONS**, the sentence “Patients with known sensitivity to verapamil hydrochloride” has been deleted.

8. In **WARNINGS AND PRECAUTIONS/Heart Failure**, passive voice has been converted to active voice. The first paragraph now reads:

Verapamil has a negative inotropic effect which, in most patients, is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In previous clinical experience with 4,954 patients primarily with immediate-release verapamil, 87 (1.8%) developed congestive heart failure or pulmonary edema. Avoid Verapamil in patients with severe left ventricular dysfunction (e.g., ejection fraction less than 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta adrenergic blocker [*see Drug Interactions (7.5)*]. Control patients with milder ventricular dysfunction, if possible, with optimum doses of digitalis and/or diuretics before verapamil treatment is started [*see Drug Interactions (7.6)*].

9. In **WARNINGS AND PRECAUTIONS/Hypotension**, the first paragraph has been revised from:

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4,954 patients enrolled in clinical trials was 2.5%. In hypertensive patients, decreases in blood pressure below normal are unusual.

Tilt table testing (60 degrees) was not able to induce orthostatic hypotension. In Verelan PM, 1.7% of the patients developed significant hypotension.

To:

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension. In hypertensive patients, decreases in blood pressure below normal are unusual. The incidence of hypotension observed in 4,954 patients enrolled in clinical trials of other verapamil formulations was 2.5%. In clinical studies of Verelan PM, 1.7% of the patients developed significant hypotension [*see Adverse Reactions (6.3)*]. Tilt table testing (60 degrees) was not able to induce orthostatic hypotension.

10. In **WARNINGS AND PRECAUTIONS**, the following cross reference has been added to the sections on **Hypotension, Atrioventricular Block, and Patients with Hypertrophic Cardiomyopathy**:

[see Adverse Reactions (6.3)]

11. In **WARNINGS AND PRECAUTIONS** the title of **Section 5.6** has been revised from:

Patients with hypertrophic cardiomyopathy (IHSS)

To:

Patients with Hypertrophic Cardiomyopathy

12. In **WARNINGS AND PRECAUTIONS/Patients with Hypertrophic Cardiomyopathy**, a reference to Idiopathic Hypertrophic subaortic stenosis (IHSS) has been added to the first sentence of the first paragraph.

13. **ADVERSE REACTIONS/Clinical Trials Experience**, the following has been added as the first paragraph:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

14. In **ADVERSE REACTIONS/Clinical Trials Experience**, Tables 1 and 2 have been assigned appropriate titles.

15. In **ADVERSE REACTIONS/Clinical Trials Experience**, the table “Elevated Liver Enzymes (See WARNINGS)” has been deleted.

16. In **ADVERSE REACTIONS/Clinical Trials Experience**, the term “digitalized patients” has been revised to “patients taking digoxin” in the first sentence of the sixth paragraph.

17. In **ADVERSE REACTIONS/Open Trials/Postmarketing Experience**, the parenthetical “(open verapamil trials, postmarketing verapamil experience [reactions added since the initial US approval of Verelan PM in 1998 are marked with an asterisk])” has been added to the first sentence of the first paragraph.
18. In **ADVERSE REACTIONS/Open Trials/Postmarketing Experience**, the following have been added to the list of adverse reactions:
- ECG Abnormal*
 - Hypertension*
 - Elevated liver enzymes* [see Warnings and Precautions (5.3)]
 - asthenia*

19. **ADVERSE REACTIONS/Treatment of Acute Cardiovascular Adverse Reactions**, passive voice has been converted to active voice. The first paragraph now reads:

The frequency of cardiovascular adverse reactions that require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, apply the appropriate emergency measures immediately; e.g., intravenously administered norepinephrine bitartrate, atropine sulfate, isoproterenol HCl (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy, use alpha-adrenergic agents (phenylephrine HCl, metaraminol bitartrate, or methoxamine HCl) to maintain blood pressure, and isoproterenol and avoid norepinephrine. If further support is necessary, inotropic agents (dopamine HCl or dobutamine HCl) may be administered. Actual treatment and dosage depends on the severity of the clinical situation and the judgment and experience of the treating physician.

20. In **ADVERSE REACTIONS/Treatment of Acute Cardiovascular Adverse Reactions**, the reference to IHSS has been deleted from the sixth sentence of the first paragraph.
21. In **DRUG INTERACTIONS**, the listing sequence has been revised in order to list the drug interactions from most important to least important.
22. In **DRUG INTERACTIONS**, the following has been added:

7.6 Clonidine

Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concurrently with verapamil. Monitor heart rate in patients receiving concomitant verapamil and clonidine.

7.7 Telithromycin

Hypotension and bradyarrhythmias have been observed in patients receiving concurrent telithromycin, an antibiotic in the ketolide class of antibiotics.

23. In **Drug INTERACTIONS/CYP3A4 Inhibitors and Inducers**, “Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent telithromycin, an antibiotic in the ketolide class of antibiotics” has been added.

24. In **DRUG INTERACTIONS/Grapefruit Juice**, the term “PK” has been changed to “Pharmacokinetics.”

25. In **DRUG INTERACTIONS/Digitalis**, passive voice has been converted to active voice. The first paragraph now reads:

Clinical use of verapamil in patients taking digoxin has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, 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. In patients with hepatic cirrhosis the influence of verapamil on digoxin pharmacokinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digoxin by 27% and 29%, respectively. Reduce maintenance and digitalization doses when verapamil is administered, and reassess the patient to avoid over- or underdigitalization. Whenever overdigitalization is suspected, reduce the daily dose of digoxin or temporarily discontinued. On discontinuation of verapamil use, reassess the patient to avoid underdigitalization. In previous clinical trials with other verapamil formulations related to the control of ventricular response in patients taking digoxin who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients, and asymptomatic hypotension occurred in 5% of patients.

26. In **DRUG INTERACTIONS/Digitalis**, the term “kinetics” has been changed to “pharmacokinetics.”

27. In **DRUG INTERACTIONS/Antineoplastic Agents** has been changed from:

Verapamil can increase the efficacy of doxorubicin both in tissue culture systems and in patients. It raises the serum doxorubicin levels. The absorption of verapamil can be reduced by the cyclophosphamide, oncovin, procarbazine, prednisone (COPP) and the vindesine, adriamycin, cisplatin (VAC) cytotoxic drug regimens. Concomitant administration of R verapamil can decrease the clearance of paclitaxel.

To:

Verapamil can increase doxorubicin levels. The absorption of verapamil can be reduced by the cyclophosphamide, oncovin, procarbazine, prednisone (COPP) and the vindesine, adriamycin, cisplatin (VAC) cytotoxic drug regimens. Concomitant administration of R verapamil can decrease the clearance of paclitaxel.

28. In **DRUG INTERACTIONS/Quinidine**, passive voice has been converted to active voice. The paragraph now reads:

In a small number of patients with hypertrophic cardiomyopathy, concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, avoid combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy.

29. In **DRUG INTERACTIONS/Antihypertensive Agents**, passive voice has been converted to active voice. The paragraph now reads:

Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers) will usually have an additive effect on lowering blood pressure. Monitor patients receiving these combinations appropriately. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

30. In **DRUG INTERACTIONS/Disopyramide**, passive voice has been converted to active voice. The paragraph now reads:

Until data on possible interactions between verapamil and disopyramide are obtained, do not administer disopyramide within 48 hours before or 24 hours after verapamil administration.

31. In **DRUG INTERACTIONS/Inhalation Anesthetics**, passive voice has been converted to active voice. The paragraph now reads:

Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, titrate slowly to avoid excessive cardiovascular depression.

32. In **USE IN SPECIFIC POPULATIONS/Pregnancy**, “Verapamil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus” has been added as the sixth sentence.

33. In **USE IN SPECIFIC POPULATIONS/Nursing Mothers**, the paragraph has been revised from:

Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

To:

Verapamil is excreted into human milk. In case studies where verapamil concentration in human milk was calculated, the nursing infant doses ranged from less than 0.01% to 0.1% of the mother’s verapamil dose. Consider possible infant exposure when verapamil is administered to a nursing woman.

34. In **USE IN SPECIFIC POPULATIONS/Impaired Hepatic Function**, the first paragraph has been changed from:

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 should be carried out. [*see Overdosage (10)*]

To:

Since verapamil is highly metabolized by the liver, consider lower dosages and closely monitor responses to the drug in 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. Monitor for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. [*see Overdosage (10)*]

35. In **OVERDOSAGE**, passive voice has been converted to active voice. The first and second paragraphs now read:

There is no specific antidote for verapamil overdose; treatment is supportive. Delayed pharmacodynamic consequences may occur with sustained-release formulations, and observe patients for at least 48 hours, preferably under continuous hospital care. Reported effects include hypotension, bradycardia, cardiac conduction defects, arrhythmias, hyperglycemia, and decreased mental status. In addition, there have been literature reports of noncardiogenic pulmonary edema in patients taking large overdoses of verapamil (up to approximately 9 g).

In acute overdose, consider gastrointestinal decontamination with cathartics and whole bowel irrigation. Calcium, inotropes (i.e., isoproterenol HCl, dopamine HCl, and glucagon), atropine sulfate, vasopressors (i.e., norepinephrine, and epinephrine), and cardiac pacing have been used with variable results to reverse hypotension and myocardial depression. In a few reported cases, overdose with calcium channel blockers that was initially refractory to atropine became more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride.

36. In **CLINICAL PHARMACOLOGY/Pharmacodynamics/Essential Hypertension**, the sentence “Improved left ventricular diastolic function in patients with IHSS and those with coronary heart disease has also been observed with verapamil” has been deleted from the first paragraph.
37. The **CLINICAL PHARMACOLOGY/Pharmacokinetics** section has been revised to include subsections for *Absorption*, *Distribution*, and *Metabolism and Excretion*.
38. In **PATIENT COUNSELING INFORMATION**, passive voice has been converted to active voice. The second bullet now reads:
- When the sprinkle method of administration is prescribed, explain the details of the proper technique to the patient. [*See Dosage and Administration (2.2)*]
39. The manufacturing Information has been updated to read:

Schwarz Pharma, LLC, a
Subsidiary of UCB, Inc.
Smyrna, GA 30080

40. There are minor editorial revisions throughout (i.e. the capitalization of the letters PM in the name of the drug and ^{®TM} added after the word CODAS).

We have completed our review of this application, as amended and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

Please resubmit the enclosed content of labeling in SPL format as soon as possible, but no later than 14 days from the date of this letter. For administrative purposes, please designate this submission, "**SPL for approved NDA 020943/S-021.**"

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D.,Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling text

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20943	SUPPL-21	ELAN DRUG DELIVERY INC	VERELAN PM (VERAPAMIL HCL)ER CAPSULES

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

/s/

Lori A WACHTER
12/16/2009

NORMAN L STOCKBRIDGE
12/16/2009