DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19614/S-034/S-045 **SUPPLEMENT APPROVAL**

Elan Drug Delivery, Inc.
Attention: Roger Wayne Wiley, RPh
Senior Director, Regulatory Affairs
1300 Gould Drive
Gainesville, GA 30504

Dear Mr. Wiley:

Please refer to your supplemental new drug applications (NDAs) dated July 10, 2002 (S-034) and October 28, 2009 (S-045) for Verelan (verapamil hydrochloride) 120mg, 180mg, 240mg and 360mg Capsules. We also refer to our approvable action letter for S-034 dated January 31, 2003.

We acknowledge the revisions in our letter dated March 14, 2003 for S-034 have been incorporated into the package insert based on your September 11, 2003 submission.

This supplemental new drug application (S-045) provides for the following revisions to the package insert:

1. Under **PRECAUTIONS, Drug-Drug Interactions,** Drug Interactions: Effects of other drugs on verapamil pharmacokinetics, a sentence was added to the end of the paragraph. It reads:

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

2. Under **PRECAUTIONS, Drug Interactions,** a new section was added that reads:

   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.

3. As agreed through informal communications, the **PRECAUTIONS, Drug Interactions,** *Digitalis*, (section 7.4) that read:

   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. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Maintenance digitalis doses should be reduced when verapamil is administered, and the patient

> should be carefully monitored to avoid over- or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digoxin should be reduced or temporarily discontinued. Upon discontinuation of verapamil HCl, the patient should be reassessed to avoid underdigitalization.

Was revised to read as follows:

> Consider reducing digoxin dose when verapamil and digoxin are to be given together. Monitor digoxin level periodically during therapy. 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. If digoxin toxicity is suspected, suspend or discontinue digoxin therapy.
>
> 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.

We have completed our review of these applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text for the package insert. For administrative purposes, please designate this submission, "SPL for approved NDA 19614/S-045."

Within 14 days from the date of this letter, please amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

> 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

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
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-19614	SUPPL-34	ELAN DRUG DELIVERY INC	VERELAN (VERAPAMIL HCL) CAPS
NDA-19614	SUPPL-45	ELAN DRUG DELIVERY INC	VERELAN (VERAPAMIL HCL) CAPS

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

/s/

MARY R SOUTHWORTH
03/30/2010