DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-145/S-015

Schering Corporation
Attention: Ms.Yvette Henderson
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Dear Ms. Henderson:

Please refer to your supplemental new drug application dated September 28, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NITRO-DUR (nitroglycerin) 0.1, 0.2, 0.3, 0.4, 0.6, and 0.8 mg/hr Transdermal Infusion System.

We acknowledge receipt of your submission dated April 15, 2004 which constituted a complete response to our July 23, 2002 approvable letter.

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

1. Under **PRECAUTIONS**, **General** subsection, the first 3 paragraphs have been revised as follows:

   Severe hypertension, particularly with upright posture, may occur with even small doses of nitroglycerin, particularly in the elderly. The NITRO-DUR transdermal infusion system should therefore be used with caution in elderly patients who may be volume depleted, are on multiple medications or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

   Elderly patients may be more susceptible to hypotension and may be at greater risk of falling at the therapeutic doses of nitroglycerin.

   Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy, particularly in the elderly.

2. The **PRECAUTIONS** section was revised to include a new **Geriatric Use** subsection:

   Geriatric Use: Clinical studies of NITRO-DUR Transdermal Infusion System did not include sufficient information to determine whether subjects 65 years or older respond differently from younger subjects. Additional clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may result in hypotension and increased risk of falling. In general, dose selection for the 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.

3. Under **OVERDOSAGE, Hemodynamic Effects**, a new first paragraph has been added that reads as follows:

   Nitroglycerin toxicity is generally mild. The estimated adult oral lethal dose of nitroglycerin is 200 mg to 1,200 mg. Infants may be more susceptible to toxicity from nitroglycerin. Consultation with a poison center should be considered.

4. Under **OVERDOSAGE, Methemoglobinemia**, the fourth paragraph that read "When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously" has been changed to:

   Methemoglobinemia should be treated with methylene blue if the patient develops cardiac or CNS effects of hypoxia. The initial dose is 1-2 mg/kg infused intravenously over 5 minutes. Repeat methemoglobin levels should be obtained 30 minutes later and a repeat dose of 0.5-1.0 mg/kg may be used if the level remains elevated and the patient is still symptomatic. Relative contraindications for methylene blue include known NADH methemoglobin reductase deficiency or G-6-PD deficiency. Infants under age 4 months may not respond to methylene blue due to immature NADH methemoglobin reductase. Exchange transfusion has been used successfully in critically ill patients when methemoglobinemia is refractory to treatment.

5. **Minor revisions** were noted; under **HOW SUPPLIED,**

   a) All hospital unit (100) doses were deleted.

   b) The "**CAUTION:** Federal Law prohibits dispensing without prescription**"** has been changed to Rx only.

We have completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on April 15, 2004.

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

MEDWATCH, HFD-410
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 contact:

Cheryl Ann Borden, MSN, R.N., CCRN, CCNS
Regulatory Health Project Manager
(301) 594-5315

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge

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