



NDA 20-225/S-008

Schering Corporation
Attention: Ms. Mary Jane Nehring
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Dear Ms. Nehring:

Please refer to your supplemental new drug application dated August 8, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IMDUR (isosorbide mononitrate) 30, 60 and 120 mg Extended Release Tablets.

We acknowledge receipt of your submission dated September 27, 2002 that constituted a complete response to our April 24, 2002 approvable letter.

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

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

Geriatric Use: Clinical studies of IMDUR Tablets did not include sufficient information on patients age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience for IMDUR has not identified differences in response between elderly and younger patients. Clinical experience for organic nitrates reported in the literature identified a potential for severe hypotension and increased sensitivity to nitrates in the elderly. 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.

Elderly patients may have reduced baroreceptor function and may develop severe orthostatic hypotension when vasodilators are used. IMDUR should therefore be used with caution in elderly patients who may be volume depleted, on multiple medications or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

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

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

Food and Drug Administration
Rockville MD 20857

2. Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**, the statement “No evidence of carcinogenicity was observed in mice exposed to isosorbide mononitrate in their diets for up to 104 weeks at doses of up to 900 mg/kg/day” was added after the first sentence of this subsection.
3. The header for the pregnancy subsection of the labeling was changed from **PREGNANCY** to **Pregnancy**.

Note: Items #2 and #3 above were included in the final printed labeling for S-008 in response to the Division’s supplement request letter dated August 14, 2002.

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 submitted final printed labeling (package insert included in your submission of September 27, 2002). Accordingly, the supplemental application is approved effective on the date of this letter.

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:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

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

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/s/

Doug Throckmorton
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