DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-092/SLR-015

Watson Laboratories, Inc.
Attention: Mr. Paul G. Young
417 Wakara Way
Salt Lake City, UT 84108

Dear Mr. Young:

Please refer to your supplemental new drug application dated June 6, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dilacor XR (diltiazem hydrochloride) Extended-Release 120, 180 and 240 mg Capsules.

This supplemental new drug application provides for changes to the **DESCRIPTION, OVERDOSAGE or EXAGGERATED RESPONSE** and **HOW SUPPLIED** sections of the package insert, in addition to administrative changes.

The proposed language and changes are acceptable for use as follows:

1. Under **DESCRIPTION/Inactive Ingredients**, hydroxypropyl methylcellulose was changed to hypromellose.

2. Under **OVERDOSAGE or EXAGGERATED RESPONSE**, the first paragraph has been revised from:
   Overdosage experience with oral diltiazem hydrochloride has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

   To:
   Several literature reports have identified cases of diltiazem hydrochloride overdose, some with multiple drug ingestion, with both fatal and non-fatal outcomes. The reported events affected multiple body systems including the cardiovascular system (bradycardia, complete heart block, asystole, cardiac failure, arrhythmia, atrial fibrillation, palpitations, hypotension, ischemia, ECG changes), respiratory system (respiratory failure, hypoxia, dyspnea, pulmonary edema), central nervous system (loss of conciousness, convulsions, dizziness, confusion, agitation), gastrointestinal system (nausea, vomiting), skin and appendages (increased sweating), and other systems (hypotonia, iliac artery thrombosis, metabolic acidosis, increased blood glucose). The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

3. In the table immediately under **HOW SUPPLIED,** additions were made as follows:
   a. Bottles of 30 were added under the size column for the 120, 180 and 240 mg strengths and Bottles of 1000 were added to the row of the 180 mg strength capsules.

b. The NDC numbers were updated.

Administrative changes were made at the end of the package insert as follows:

a. The prescription warning statement was changed from:
Caution: Federal law prohibits dispensing without a prescription.

to:
Rx Only.

b. The new manufacturing site was changed from:
Manufactured for: WATSON PHARMA
A Division of Watson Laboratories, Inc.
Corona, CA 91720
by Centeon LLC, Kankakee, IL 60901
was updated to read as follows:

to:
Manufactured for:
WATSON Pharma, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.
Corona, CA 92880
Manufactured by:
SkyePharma Production SAS
St-Quentin-Fallavier Cedex, France

4. The revision date and label code was updated from:
Rev. 12/97 14100 IN-1005N

to:
Rev. 05/03 14100-01

In addition, we noted editorial errors in the submitted draft labeling. When submitting final printed labeling, please correct the errors as follows:

1. In the sixth sentence under **Pharmacokinetics and Metabolism,** change the word comparative to competitive and bind to binding to read as follows:

   Competitive in vitro ligand binding studies have also shown diltiazem HCL binding is not altered by therapeutic concentrations of digoxin, HCTZ, phenylbutazone, propanalol, salicylic acid, or warfarin.

2. Under **ADVERSE REACTIONS/Hypertension/**Skin and appendages, change the word nervous to nevus to read as follows:

   Skin and appendages: Sweating, urticaria, skin hypertrophy (nevus).

3. In the second sentence under **DOSAGE and ADMINISTRATION/Concomitant Use with Other CardiovascularAgents/**Antihypertensives, replace “of” with “to” as follows:

Therefore, the dosage of diltiazem hydrochloride or the concomitant antihypertensives may need to be adjusted when adding one to the other.

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 draft labeling submitted on June 6, 2003.

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:

Ms. Denise Hinton
Regulatory Health Project Manager
(301) 594-5333.

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

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

/s/

Doug Throckmorton
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