DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA18-780/S-114

Eli Lilly and Company
Attention: Gregory Enas, PhD
Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

SUPPLEMENT APPROVAL

Dear Dr. Enas:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the product described below.

NDA No.	Supplement No.	Drug Product Name	Letter Date	Receipt Date
18-780	S-114	Humulin R (insulin human injection, USP [rDNA origin]), 500 IU/mL	5 June 2007	6 June 2007

This supplemental new drug application provides for the addition of the classes of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blocking (ARB) agents (referred to as "some kidney and blood pressure medicines" to the types of medications that may decrease insulin requirements in the MEDICATION section and the "Hypoglycemia (Low Blood Sugar)" subsection of the COMMON PROBLEMS OF DIABETES section of the patient package insert.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format and final printed labeling submitted on June 5, 2007. The text of this labeling is enclosed.

However, to more accurately reflect the mechanisms by which interaction of insulins with these drugs reduces insulin requirements, revise this labeling as described below at the time of the next printing and submit it as a "Special Supplement – Changes Being Effected" with revised SPL.

The changes to the package insert and the patient package insert are indicated below; underscoring indicates added text and strike-through indicates deleted text.

PACKAGE INSERT

Drug Interactions

The concurrent use of oral hypoglycemic agents with Humulin R (U-500) is not recommended since there are no data to support such use.

Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy (*see* CLINICAL PHARMACOLOGY).

Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

PATIENT PACKAGE INSERT (2 sections)

Medication

Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin requirements may be reduced in the presence of drugs ~~with blood-glucose-lowering activity,~~ that lower blood glucose or affect how your body responds to insulin, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, certain antidepressants and some kidney and blood pressure medicines. Your Health Care Professional may be aware of other medications that may affect your diabetes control. Therefore, always discuss any medications you are taking with your doctor.

COMMON PROBLEMS OF DIABETES

Hypoglycemia (Low Blood Sugar)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. Missing or delaying meals.
2. Taking too much insulin.
3. Exercising or working more than usual.
4. An infection or illness (especially with diarrhea or vomiting).
5. A change in the body's need for insulin.
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease.
7. Interactions with ~~other~~ certain drugs ~~that lower blood glucose~~, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, certain antidepressants and some kidney and blood pressure medicines.
8. Consumption of alcoholic beverages.

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
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

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, call Enid Galliers, Chief, Project Management Staff, at 301-796-1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
NDA 18-780/S-114: PI+PPI vial

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

/s/

Mary Parks

9/10/2007 12:05:21 PM