



NDA 20-563/S-065; NDA 21-017/S-030; NDA 21-018/S-041

Eli Lilly and Company
Attention: William Current, PhD
Senior Associate Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

SUPPLEMENT APPROVAL

Dear Dr. Current:

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

NDA	Supplement	Drug Product Name	Letter Date	Receipt Date	Amendment Dates
20-563	S-065	Humalog (insulin lispro injection [rDNA origin])	28 Oct 2005	28 Oct 2005	7 Dec 2006 10 Aug 2007 21 Aug 2007
21-017	S-030	Humalog Mix 75/25 (75% insulin lispro protamine suspension/25% insulin lispro injection [rDNA origin])	28 Oct 2005	28 Oct 2005	7 Dec 2006 10 Aug 2007 21 Aug 2007
21-018	S-041	Humalog Mix 50/50 (50% insulin lispro protamine suspension/50% insulin lispro injection [rDNA origin])	7 Dec 2006	8 Dec 2006	10 Aug 2007 21 Aug 2007

We acknowledge receipt of your amendments listed above.

These supplemental new drug applications provide for updating and consolidating the language in the physician and patient labeling for the insulin products listed above.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor agreed-upon, editorial revisions listed below to the enclosed labeling.

To more accurately reflect the mechanisms by which the interaction of insulins with angiotensin-converting-enzyme inhibitors and angiotensin II receptor blocking agents reduces insulin requirements, incorporate the changes indicated below in the enclosed labeling.

PACKAGE INSERT

Drug Interactions

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 **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 **certain** drugs, 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.

CONTENT OF LABELING

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)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to, except for including the revisions listed

above, the enclosed labeling (text for the three package inserts and text for the seven patient package inserts.) Upon receipt, we will transmit those versions to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 20-563/S-065; NDA 21-017/S-030; NDA 21-018/S-041.**”

Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letters to both the NDAs 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

Enclosures:

NDA 20-563/S-065 PI
NDA 20-563/S-065 PPI-vial
NDA 20-563/S-065 PPI-Pen
NDA 20-563/S-065 PPI-cartridge
NDA 21-017/S-030 PI
NDA 21-017/S-030 PPI-vial
NDA 21-017/S-030 PPI-Pen
NDA 21-018/S-041 PI
NDA 21-018/S-041 PPI-vial
NDA 21-018/S-041 PPI-Pen

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

/s/

Hylton Joffe
8/22/2007 05:54:39 PM
Hylton Joffe for Mary Parks