HUMALOG® PEN

insulin lispro injection (rDNA origin)

Eli Lilly and Company

06/24/2003

HUMALOG® is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than human regular insulin. Therefore, in patients with type 1 diabetes, Humalog should be used in regimens that include a longer-acting insulin. However, in patients with type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents. Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or one of its excipients.
## CONTENTS

<table>
<thead>
<tr>
<th>Reviews / Information Included in this NDA Review.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
</tr>
<tr>
<td>Other Action Letters</td>
</tr>
<tr>
<td>Labeling</td>
</tr>
<tr>
<td>REMS</td>
</tr>
<tr>
<td>Summary Review</td>
</tr>
<tr>
<td>Officer/Employee List</td>
</tr>
<tr>
<td>Office Director Memo</td>
</tr>
<tr>
<td>Cross Discipline Team Leader Review</td>
</tr>
<tr>
<td>Medical Review(s)</td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
</tr>
<tr>
<td>Environmental Assessment</td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
</tr>
<tr>
<td>Statistical Review(s)</td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
</tr>
<tr>
<td>Clinical Pharmacology/Biopharmaceutics Review(s)</td>
</tr>
<tr>
<td>Other Reviews</td>
</tr>
<tr>
<td>Risk Assessment and Risk Mitigation Review(s)</td>
</tr>
<tr>
<td>Proprietary Name Review(s)</td>
</tr>
<tr>
<td>Administrative/Correspondence Document(s)</td>
</tr>
</tbody>
</table>
NDA 20-563/S-040

Eli Lilly and Company
Attention: Jeffrey L. Winn, D.D.S., R.Ph.
Senior Regulatory Research Scientist
U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Winn:

Please refer to your supplemental new drug application dated February 10, 2003, received
February 11, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act
for Humalog (insulin lispro [rDNA origin] injection).

We acknowledge receipt of your submission dated April 9, 2003.

This “Changes Being Effected” supplemental new drug application provides for an addition of
tamper evident tape with the text “If the seal is broken before first use, contact pharmacist”
added to the 3 mL disposable insulin delivery devices (HP 8725, Humalog Pen) carton label.

We 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 9, 2003.

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, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Carton label (circular SH 8712 FSAMS) submitted on April 9, 2003
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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David Orloff
6/24/03 01:23:43 PM
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 020563/S-040

LABELING
Humalog® Pen
insulin lispro injection
(rDNA origin)

Rx

This device is suitable for use with Becton Dickinson and Company's insulin pen needles or their equivalent (needles not included).

Rx only

5 x 3 mL disposable insulin delivery devices
3 mL
100 units per mL
HP 8725
U-100

If the seal is broken before first use, contact pharmacist

Keep in a cold place. Avoid freezing.

Warning: Any change of insulin should be made cautiously and only under medical supervision.

For subcutaneous use,

See enclosed insert for dosage.

Each mL contains 100 Units of insulin lispro; glycerin, 16 mg; dibasic sodium phosphate, 1.88 mg; Metacresol, 3.15 mg; zinc oxide content adjusted to provide 0.0187 mg zinc ion; trace amounts of phenol, and water for injection. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

Neutral

Manufactured by Lilly France S.A.S.
F-67640 Fegersheim, France
for Eli Lilly and Company
Indianapolis, IN 46285, USA
1-888-885-4559

IMPORTANT - SEE WARNINGS ON ENCLOSED INSERT

First use, contact pharmacist

For information call 1-888-885-4559
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 020563/S-040

OTHER REVIEW(S)
Division of Metabolic and Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: 20-563/-040

Name of Drug: Humalog (insulin lispro [rDNA origin] injection)

Applicant: Eli Lilly

Material Reviewed: Carton label for 3 mL disposable insulin delivery device (Humalog Pen)

Submission Date: February 10 and April 9, 2003

Background and Summary:

This supplement provides for an addition of tamper evident tape with the text added to the carton: “If the seal is broken before first use, contact pharmacist”.

A supplement for 3 mL disposable insulin delivery device (Humalog Pen) was first submitted under S-006 on September 5, 1997, and approved on August 6, 1998.

Review:

The final printed carton label (SH 8712 FSAMS) of this supplement (S-040) is compared to the last approved carton label under S-006 (SH 8710 FSAMS) and found the following changes:

1. Added the text “If the seal is broken before first use, contact pharmacist” in red and bolded fonts.

   This change is acceptable since the supplement provides for this change.

2. Added the following phrase “Manufactured by Lilly Frances S.A.S. F-67640 Fegersheim, France for”.

   This change is acceptable per Dr. Stephen Moore, Chemistry Team Leader. Cartridges used in insulin Pens are manufactured at Lilly’s facility in Fegersheim, France.

Conclusions:

Issue an approval letter.

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

/s/
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Julie Rhee
6/23/03 03:58:56 PM
CSO
Eli Lilly and Company  
Attention: Jeffrey L. Winn, D.D.S., R.Ph.  
Senior Regulatory Research Scientist  
US Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Winn:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following products:

<table>
<thead>
<tr>
<th>NDA Number</th>
<th>Supplement Number</th>
<th>Name of Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-781</td>
<td>S-072</td>
<td>Humulin N (human insulin [rDNA origin] isophane suspension)</td>
</tr>
<tr>
<td>19-717</td>
<td>S-052</td>
<td>Humulin 70/30 (70% human insulin isophane suspension and 30% human insulin injection, [rDNA origin])</td>
</tr>
<tr>
<td>20-563</td>
<td>S-040</td>
<td>Humalog (insulin lispro [rDNA origin] injection)</td>
</tr>
<tr>
<td>21-017</td>
<td>S-010</td>
<td>Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25 insulin lispro injection, [rDNA origin])</td>
</tr>
</tbody>
</table>

Date of supplement: February 10, 2003  
Date of receipt: February 11, 2003

These supplemental applications, submitted as “Supplement - Changes Being Effected” propose the addition of tamper evident tape with the text “If the seal is broken before first use, contact...” added to the Pen carton of the insulin products mentioned above.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 12, 2003, in accordance with 21 CFR 314.101(a).
All communications concerning these supplements should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6424.

Sincerely,

(See appended electronic signature page)

Julie Rhee
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
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/

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Julie Rhee
2/13/03 10:14:56 AM