CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-017/ S-002

Trade Name: Humalog Mix, 75/25

Generic Name: Insulin Lispro [rDNA origin]

Sponsor: Ely Lilly and Company

Approval Date: February 8, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-017/s-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-017/s-002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-017/S-002
NDA 21-018/S-001

Eli Lilly and Company
Attention: Gregory G. Enas, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Enas:

Please refer to your supplemental new drug applications dated May 15, 2000, received May 17, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following products:

NDA 21-017/S-002	Humalog® Mix 75/25 (75% insulin lispro [rDNA origin] protamine suspension and 25% insulin lispro [rDNA origin] injection)
NDA 21-018/S-001	Humalog® Mix 50/50 (50% insulin lispro [rDNA origin] protamine suspension and 50% insulin lispro [rDNA origin] injection)

These "Changes Being Effected" supplemental new drug applications provide for labeling changes to the Disposable Insulin Delivery Device User Manual.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (device user manual submitted May 15, 2000). Accordingly, these supplemental applications are approved effective on the date of this letter.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

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

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

/s/

David Orloff
2/8/02 05:51:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-017/s-002

APPROVED LABELING

5.01 PA 9235 FSAMP

INFORMATION FOR THE PATIENT
3 ML DISPOSABLE INSULIN DELIVERY DEVICE

HUMALOG® Mix75/25™ Pen
75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN)
100 UNITS PER ML (U-100)

WARNINGS

THIS LILLY HUMAN INSULIN ANALOG MIXTURE IS DIFFERENT FROM OTHER INSULIN MIXTURES IN THAT ITS ONSET OF ACTION IS VERY QUICK. THE QUICK ONSET OF ACTION MEANS THAT YOU SHOULD TAKE YOUR DOSE OF HUMALOG® Mix75/25™ (75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION, [rDNA ORIGIN]) WITHIN 15 MINUTES BEFORE YOU EAT.

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN), OR METHOD OF MANUFACTURE (rDNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN THE TIMING OR DOSAGE OF HUMALOG Mix75/25.

PATIENTS TAKING HUMALOG Mix75/25 MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH OTHER INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.

TO OBTAIN AN ACCURATE DOSE, CAREFULLY READ AND FOLLOW THE "DISPOSABLE INSULIN DELIVERY DEVICE USER MANUAL" AND THIS "INFORMATION FOR THE PATIENT" INSERT BEFORE USING THIS PRODUCT.

BEFORE EACH INJECTION, YOU SHOULD PRIME THE PEN, A NECESSARY STEP TO MAKE SURE THE PEN IS READY TO DOSE. PRIMING THE PEN IS IMPORTANT TO CONFIRM THAT INSULIN COMES OUT WHEN YOU PUSH THE INJECTION BUTTON AND TO REMOVE AIR THAT MAY COLLECT IN THE INSULIN CARTRIDGE DURING NORMAL USE. IF YOU DO NOT PRIME, YOU MAY RECEIVE TOO MUCH OR TOO LITTLE INSULIN (*see also* INSTRUCTIONS FOR INSULIN PEN USE section).

DIABETES

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs.

To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near-normal level. You have been instructed to test your blood and/or urine regularly for glucose. Studies have shown that some chronic complications of diabetes such as eye disease, kidney disease, and nerve disease can be significantly reduced if the blood sugar is maintained as close to normal as possible. The American Diabetes Association recommends that if your pre-meal glucose levels are consistently above 130 mg/dL, bedtime glucose levels are

consistently above 160 mg/dL or your hemoglobin A_{1c} (HbA_{1c}) is more than 7%, consult your doctor. A change in your diabetes therapy may be needed. If your blood tests consistently show below-targeted glucose levels, you should also let your doctor know. Proper control of your diabetes requires close and constant cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly, and take your insulin injections as prescribed.

Always keep an extra Humalog Mix75/25 Pen as well as a spare needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

HUMALOG Mix75/25

Description

Humalog (insulin lispro [rDNA origin]) is made by a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for this human insulin analog. Humalog Mix75/25 is a mixture of 75% insulin lispro protamine suspension and 25% insulin lispro. It is a longer-acting insulin combined with the more rapid onset of action of Humalog. The duration of activity is similar to that of Humulin® 70/30 and may last up to 24 hours following injection. The time course of Humalog Mix75/25 action, like that of other insulins, may vary in different individuals or at different times in the same individual, based on dose, site of injection, blood supply, temperature, and physical activity. Humalog Mix75/25 is a sterile suspension and is for subcutaneous injection. It should not be used intravenously. The concentration of Humalog Mix75/25 is 100 units/mL (U-100).

Humalog Mix75/25 starts lowering blood glucose more quickly than regular human insulin, allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast, mixtures containing regular human insulin should be given 30 to 60 minutes before a meal.

Identification

Insulin lispro (rDNA origin) injection ~~(rDNA origin)~~, by Eli Lilly and Company, has the trademark Humalog. Humalog products are available in two formulations — Humalog and Humalog Mix75/25. Your doctor has prescribed the type of insulin that he/she believes is best for you.

DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION. YOU SHOULD NOT MIX HUMALOG Mix75/25 WITH ANOTHER INSULIN.

The Humalog Mix75/25 Pen is available in boxes of 5 disposable insulin delivery devices ("insulin Pens"). The Humalog Mix75/25 Pen is not designed to allow any other insulin to be mixed in its cartridge of Humalog Mix75/25, or for the cartridge to be removed.

Always examine the appearance of Humalog Mix75/25 suspension in the insulin Pen before administering a dose. Roll the Pen between the palms 10 times (*see* Figure 1). Holding the Pen by one end, invert it 180° slowly 10 times to allow the small glass bead to travel the full length of the cartridge with each inversion (*see* Figure 2).

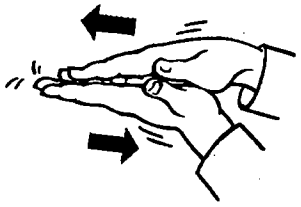


Figure 1.

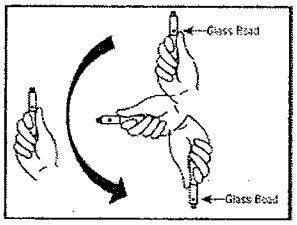


Figure 2.

Humalog Mix75/25 should look uniformly cloudy or milky after mixing. If not, repeat the above steps until the contents are mixed. Pens containing Humalog Mix75/25 suspension should

be examined frequently. Do not use if the insulin substance (the white material) remains visibly separated from the liquid after mixing. Do not use a Humalog Mix75/25 Pen if there are clumps in the insulin after mixing. Do not use a Humalog Mix75/25 Pen if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance. Always check the appearance of the Humalog Mix75/25 suspension before using. If you note anything unusual in its appearance or notice your insulin requirements changing markedly, consult your doctor.

Storage

Not in-use (unopened): Humalog Mix75/25 Pens not in-use should be stored in a refrigerator but not in the freezer. Do not use Humalog Mix75/25 Pen is it has been frozen.

In-use: Humalog Mix75/25 Pens in-use should **NOT** be refrigerated but should be kept at room temperature (below 86°F [30°C]) away from direct heat and light. Humalog Mix75/25 Pens in-use must be discarded **after 10 days,** even if they still contain Humalog Mix75/25.

Do not use Humalog Mix75/25 Pens after the expiration date stamped on the label.

INSTRUCTIONS FOR INSULIN PEN USE

It is important to read, understand, and follow the instructions in the "Disposable Insulin Delivery Device User Manual" before using. Failure to follow instructions may result in getting too much or too little insulin. The needle must be changed and the Pen must be primed before each injection to make sure the Pen is ready to dose. Performing these steps before each injection is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use.

Every time you inject:

- **Use a new needle.**
- **Prime to make sure the Pen is ready to dose.**
- **Make sure you got your full dose.**

NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES.

PREPARING THE INSULIN PEN FOR INJECTION

1. Inspect the appearance of Humalog Mix75/25 suspension in the Humalog Mix75/25 Pen. It should look uniformly cloudy or milky after mixing. Once the Humalog Mix75/25 Pen is in use, inspect the insulin in the Humalog Mix75/25 Pen before each injection.
2. Follow the instructions in the "Disposable Insulin Delivery Device User Manual" for these steps:
   - Preparing the Pen
   - Attaching the Needle. **Use a new needle for each injection.**
   - Priming the Pen. **The Pen must be primed before each injection to make sure the Pen is ready to dose.** Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use.
   - Setting a Dose
   - Injecting a Dose. **To make sure you have received your full dose, you must push the injection button all the way down until you see a diamond (◆) or an arrow (→) in the center of the dose window.**
   - Following an Injection

PREPARING FOR INJECTION

1. Wash your hands.
2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the previous injection site. The usual sites of injection are abdomen, thighs, and arms.
3. Cleanse the skin with alcohol where the injection is to be made.
4. With one hand, stabilize the skin by spreading it or pinching up a large area.
5. Inject the dose as instructed by your doctor. Hold the needle under the skin for at least 5 seconds after injecting.

6. After injecting a dose, pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.**
7. Immediately after an injection, remove the needle from the Humalog Mix75/25 Pen. Doing so will guard against contamination, and prevent leakage of Humalog Mix75/25, reentry of air, and needle clogs. **Do not reuse needles.** Place the used needle in a puncture-resistant disposable container and properly dispose of it as directed by your Health Care Professional.

DOSAGE

Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you. Your usual Humalog Mix75/25 dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your Humalog Mix75/25 dose are:

Illness

Illness, especially with nausea and vomiting, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood glucose/urine glucose and ketones frequently and call your doctor as instructed.

Pregnancy

Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or are nursing a baby, consult your doctor. Humalog Mix75/25 has not been tested in pregnant or nursing women.

Medication

Insulin requirements may be increased if you are taking other drugs with hyperglycemic 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, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, and certain antidepressants. Your Health Care Professional is aware of these and other medications that may affect your diabetes control. Therefore, always discuss any medications you are taking with your doctor.

Exercise

Exercise may lower your body's need for insulin products during and for some time after the physical activity. Exercise may also speed up the effect of a Humalog Mix75/25 dose, especially if the exercise involves the area of your injection site. Discuss with your doctor how you should adjust your regimen to accommodate exercise.

Travel

Persons traveling across more than 2 time zones should consult their doctor concerning adjustments in their insulin schedule.

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 drugs that lower blood glucose, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants.
8. Consumption of alcoholic beverages.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

Therefore, it is important that assistance be obtained immediately.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, changing insulin preparations, or intensified control (3 or more injections per day) of diabetes. A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility.

You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia and Diabetic Ketoacidosis (DKA)

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin. Hyperglycemia can be brought about by any of the following:

1. Omitting your insulin or taking less than the doctor has prescribed.
2. Eating significantly more than your meal plan suggests.
3. Developing a fever, infection, or other significant stressful situation.

In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in DKA. The first symptoms of DKA usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath.

With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach pains, dehydration, loss of consciousness, or death. Therefore, it is important that you obtain medical assistance immediately.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

Allergy

Local Allergy — Patients occasionally experience redness, swelling, and itching at the site of injection. This condition, called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. If you have local reactions, contact your doctor.

Systemic Allergy — Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction, notify a doctor immediately.

ADDITIONAL INFORMATION

Additional information about diabetes may be obtained from your diabetes educator.

DIABETES FORECAST is a magazine designed especially for people with diabetes and their families. It is available by subscription from the American Diabetes Association (ADA), P.O. Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383).

Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRFI), 120 Wall Street 19th Floor, New York, NY 10005, 1-800-533-CURE (1-800-533-2873).

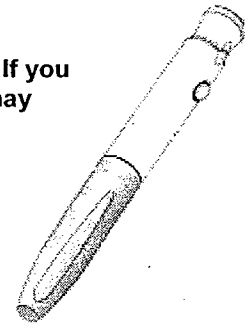
Additional information about Humalog Mix75/25 and Humalog Mix75/25 Pens can be obtained by calling The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979).

Literature revised XXX, 2004

Manufactured by Lilly France S.A.S.
F-67640 Fegersheim, France
For Eli Lilly and Company
Indianapolis, IN 46285, USA

5.01 PA 9235 FSAMP

Lilly
Disposable Insulin Delivery Device
User Manual



Instructions for Use
Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.

Every time you inject:

- **Use a new needle**
- **Prime to make sure the Pen is ready to dose**
- **Make sure you got your full dose (see page 18)**

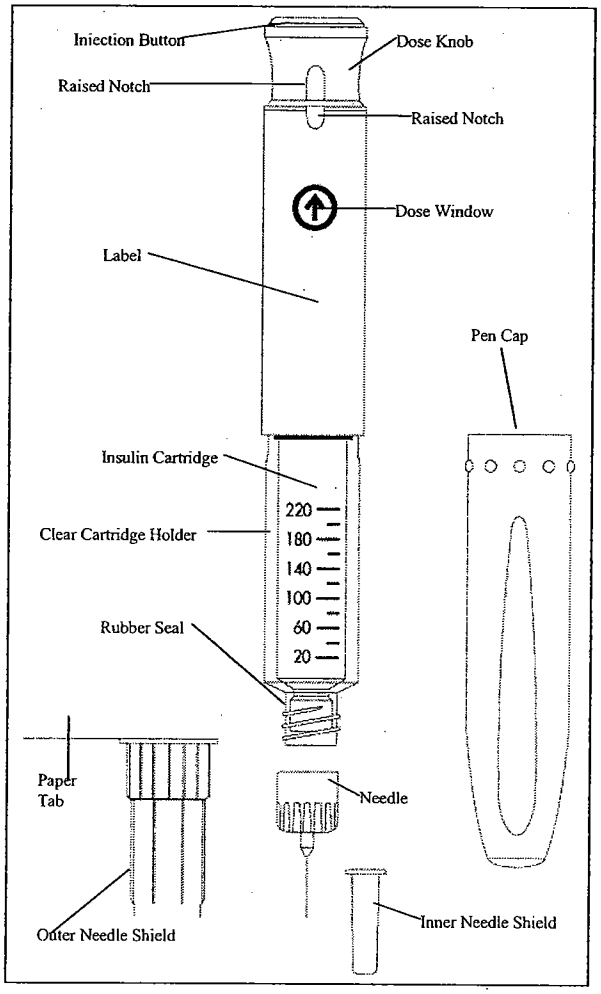
Also, read the *Information for the Patient* insert enclosed in your Pen box.

Pen Features

- A multiple dose, disposable insulin delivery device ("insulin Pen") containing 3 mL (300 units) of U-100 insulin
- Delivers up to 60 units per dose
- Doses can be dialed by single units

Table of Contents

Pen Parts


Injection Button
Dose Knob
Raised Notch
Raised Notch
Dose Window
Label
Pen Cap
Insulin Cartridge
220
180
140
100
60
20
Clear Cartridge Holder
Rubber Seal
Paper Tab
Needle
Outer Needle Shield
Inner Needle Shield

Important Notes

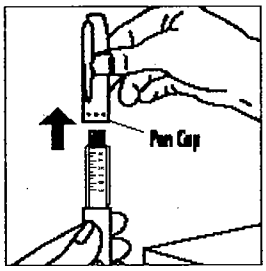
- **Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.**
- **Use a new needle for each injection.**
  - **Be sure a needle is completely attached to the Pen before priming, setting the dose and injecting your insulin.**
- **Prime every time.**
  - **The Pen must be primed before each injection to make sure the Pen is ready to dose.** Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use. **See Section III. "Priming the Pen", pages 10-13.**
  - **If you do not prime, you may get too much or too little insulin.**
  - **Make sure you get your full dose.**
  - To make sure you get your full dose, you must push the injection button all the way down until you see a diamond (♦) or an arrow (→) in the center of the dose window. See "Following an Injection", page 18.
- The numbers on the clear cartridge holder give an estimate of the amount of insulin remaining in the cartridge. Do not use these numbers for measuring an insulin dose.
- Do not share your Pen.
- Keep your Pen out of the reach of children.
- Pens that have not been used (unopened) should be stored in a refrigerator but not in a freezer. Do not use a Pen if it has been frozen. Refer to the INFORMATION FOR THE PATIENT insert for complete storage instructions.

Important Notes
(Continued)

- After a Pen is used for the first time, it should **NOT** be refrigerated but should be kept at room temperature [below 86°F (30°C)] and away from direct heat and light.
- An unrefrigerated Pen should be discarded according to the time specified in the *Information for the Patient* insert, even if it still contains insulin.
- Never use a Pen after the expiration date stamped on the label.
- Do not store your Pen with the needle attached. Doing so may allow insulin to leak from the Pen and air bubbles to form in the cartridge. Additionally, with suspension (cloudy) insulins, crystals may clog the needle.
- Always carry an extra Pen in case yours is lost or damaged.
- Dispose of empty Pens as instructed by your Health Care Professional and without the needle attached.
- This Pen is not recommended for use by blind or visually impaired persons without the assistance of a person trained in the proper use of the product.
- The directions regarding needle handling are not intended to replace local, Health Care Professional, or institutional policies.
- **Any changes in insulin should be made cautiously and only under medical supervision.**

I. Preparing the Pen

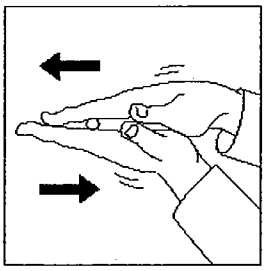
1. Before proceeding, refer to the INFORMATION FOR THE PATIENT insert for instructions on checking the appearance of your insulin.
2. Check the label on the Pen to be sure the Pen contains the type of insulin that has been prescribed for you.
3. Always wash your hands before preparing your Pen for use.
4. Pull the Pen cap to remove.



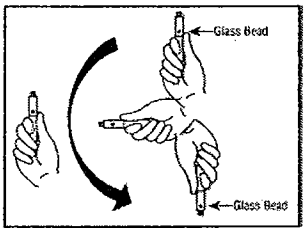
I. Preparing the Pen (Continued)

5. If your insulin is a suspension (cloudy):

   a. Roll the Pen back and forth 10 times then perform step b.

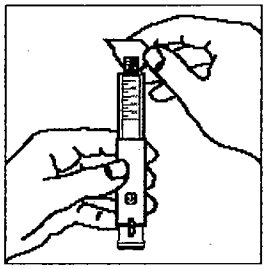


   b. Gently turn the Pen up and down 10 times until the insulin is evenly mixed.



Note: Suspension (cloudy) insulin cartridges contain a small glass bead to assist in mixing.

6. Use an alcohol swab to wipe the rubber seal on the end of the Pen.

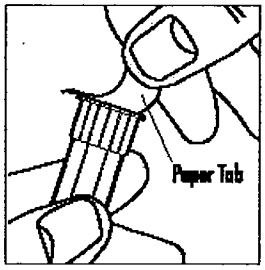


II. Attaching the Needle

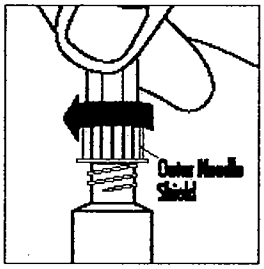
This device is suitable for use with Becton Dickinson and Company's insulin pen needles.

1. **Always use a new needle for each injection. Do not push injection button without a needle attached. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**

2. Remove the paper tab from the outer needle shield.

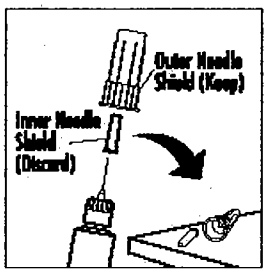


3. Attach the capped needle onto the end of the Pen by turning it clockwise until tight.



II. Attaching the Needle (Continued)

4. Hold the Pen with the needle pointing up and remove the **outer needle shield. Keep it to use during needle removal.**

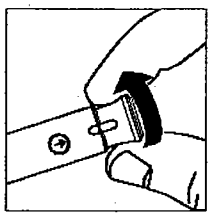


5. **Remove the inner needle shield and discard.**

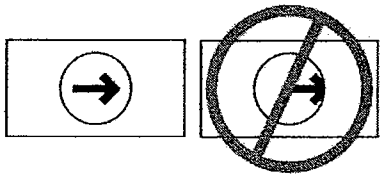
III. Priming the Pen

- **The Pen must be primed before each injection to make sure the Pen is ready to dose.** Performing the priming step is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use.
- **If you do not prime, you may get too much or too little insulin.**
- **Always use a new needle for each injection.**

1. Make sure the arrow is in the center of the dose window as shown.



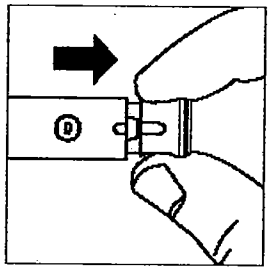
2. If you do not see the arrow in the center of the dose window, push in the injection button fully and turn the dose knob until the arrow is seen in the center of the dose window.



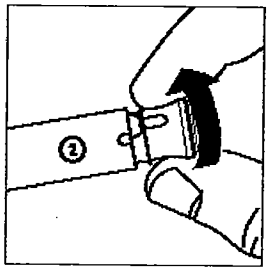
Correct

III. Priming the Pen (Continued)

3. With the arrow in the center of the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window.

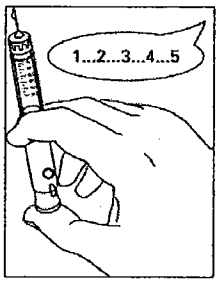


4. Turn the dose knob clockwise until the number "2" is seen in the dose window. If the number you have dialed is too high, simply turn the dose knob backward until the number 2 is seen in the dose window.



III. Priming the Pen (Continued)

5. Hold your Pen with the needle pointing up. Tap the clear cartridge holder gently with your finger so any air bubbles collect near the top.

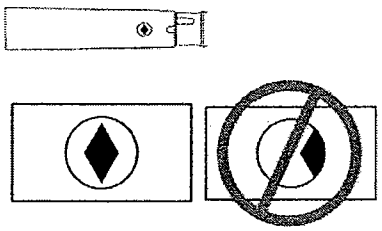


Using your thumb, if possible, push in the injection button completely. Keep pressing and continue to hold the injection button **firmly** while counting **slowly** to 5. You should see either a drop or a stream of insulin come out of the tip of the needle.

If insulin does not come out of the tip of the needle, repeat steps 1 through 5. If after several attempts insulin does not come out of the tip of the needle, change the needle and repeat the priming steps.

III. Priming the Pen (Continued)

6. At the completion of the priming step, a diamond (♦) must be seen in the center of the dose window. If a diamond (♦) is not seen in the center of the dose window, continue pushing on the injection button until you see a diamond (♦) in the center of the dose window.



Correct

Note: A small air bubble may remain in the cartridge after the completion of the priming step. If you have properly primed the Pen, this small air bubble will not affect your insulin dose.

7. Now you are ready to set your dose. See next page.

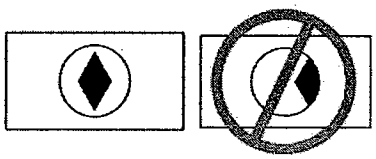
IV. Setting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**

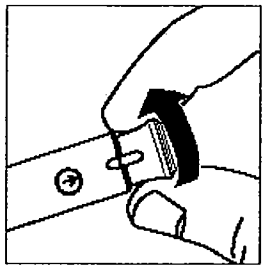
- **Caution: Do not push in the injection button while setting your dose. Failure to follow these instructions carefully may result in getting too much or too little insulin. If you accidentally push the injection button while setting your dose, you must prime the Pen again before injecting your dose. See Section III. "Priming the Pen", pages 10-13.**

1. A diamond must be seen in the center of the dose window before setting your dose.

   If you do not see a diamond in the center of the dose window, the Pen has not been primed correctly and you are not ready to set your dose. Before continuing, repeat the priming steps.

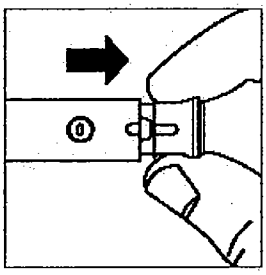


2. Turn the dose knob clockwise until the arrow (→) is seen in the center of the dose window and the notches on the Pen and dose knob are in line.

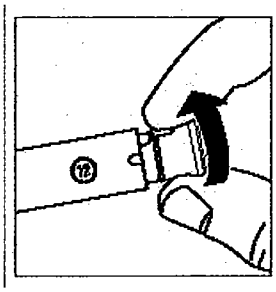


IV. Setting a Dose (Continued)

3. With the arrow (→) in the center of the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window. A dose cannot be dialed until the dose knob is pulled out.



4. Turn the dose knob clockwise until your dose is seen in the dose window. If the dose you have dialed is too high, simply turn the dose knob backward until the correct dose is seen in the dose window.



5. If you cannot dial your full dose, see the "Questions and Answers" section, Question 5, at the end of this manual.

V. Injecting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**

- **Caution: Do not attempt to change the dose after you begin to push in the injection button. Failure to follow these instructions carefully may result in getting too much or too little insulin.**

- **The effort needed to push in the injection button may increase while you are injecting your insulin dose. If you cannot completely push in the injection button, refer to the "Questions and Answers" section, Question 7, at the end of this manual.**

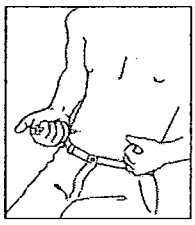
- Do not inject a dose unless the Pen is primed, just before injection, or you may get too much or too little insulin.

- If you have set a dose and pushed in the injection button without a needle attached or if no insulin comes out of the needle, see the "Questions and Answers" section, Questions 1 and 2.

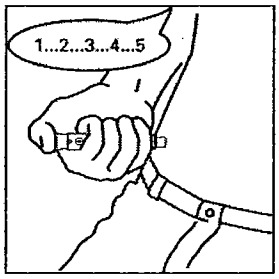
V. Injecting a Dose (Continued)

1. Wash hands. Prepare the skin and use the injection technique recommended by your Health Care Professional.

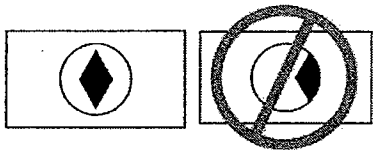
2. Insert the needle into your skin. Inject the insulin by using your thumb, if possible, to push in the injection button completely.



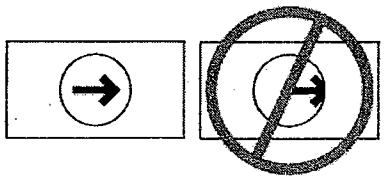
3. Keep pressing and continue to hold the injection button **firmly** while counting **slowly** to 5.



4. When the injection is done, a diamond (♦) or arrow (→) must be seen in the center of the dose window. This means your full dose has been delivered. **If you do not see the diamond or arrow in the center of the dose window, you did not get a full dose. Contact your Health Care Professional for additional instruction.**



Correct

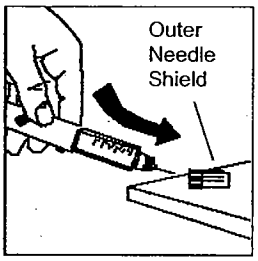


Correct

VI. Following an Injection

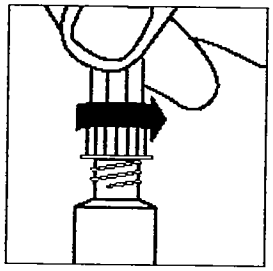
1. Make sure you got your full dose by checking that the injection button has been completely pushed in and you can see a diamond (♦) or arrow (→) in the center of the dose window. If you do not see the diamond (♦) or arrow (→) in the center of the dose window, you have not received your full dose. Contact your Health Care Professional for additional instructions.

2. Carefully replace the **outer needle shield** as instructed by your Health Care Professional.

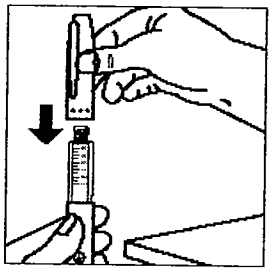


VI. Following an Injection (Continued)

3. Remove the capped needle by turning it counterclockwise. Place the used needle in a puncture-resistant disposable container and properly throw it away as directed by your Health Care Professional.



4. Replace the cap on the Pen.



5. The Pen that you are currently using should be kept at a temperature below 86°F (30°C) and away from heat and light. It should be discarded according to the time specified in the INFORMATION FOR THE PATIENT insert, even if it still contains insulin.

Do not store or dispose of the Pen with a needle attached. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.

Questions and Answers

Problem	Action
1. Dose dialed and injection button pushed in without a needle attached.	To obtain an accurate dose you must: 1) Attach a new needle. 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (→) is seen in the center of the dose window. 3) Prime the Pen.
2. Insulin does not come out of the needle.	To obtain an accurate dose you must: 1) Attach a new needle. 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (→) is seen in the center of the dose window. 3) Prime the Pen. See Section III. "Priming the Pen", pages 10-13.

Questions and Answers
(Continued)

Problem	Action
3. Wrong dose (too high or too low) dialed.	If you have not pushed in the injection button, simply turn the dose knob backward or forward to correct the dose.
4. Not sure how much insulin remains in the cartridge.	Hold the Pen with the needle end pointing down. The scale (20 units between marks) on the clear cartridge holder shows an estimate of the number of units remaining. **These numbers should not be used for measuring an insulin dose.**

Questions and Answers
(Continued)

Problem	Action
5. Full dose cannot be dialed.	The Pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the Pen you will not be able to dial past 25. Do not attempt to dial past this point. (The insulin that remains is unusable and not part of the 300 units.) If a partial dose remains in the Pen you may either: 1) Give the partial dose and then give the remaining dose using a new Pen, or 2) Give the full dose with a new Pen.
6. A small amount of insulin remains in the cartridge but a dose cannot be dialed.	The Pen design prevents the cartridge from being completely emptied. The Pen has delivered 300 units of usable insulin.

Questions and Answers (Continued)

Problem	Action
7. Cannot completely push in the injection button when priming the Pen or injecting a dose.	1) Needle is not attached or is clogged. a. Attach a new needle. b. Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or arrow (→) is seen in the center of the dose window. c. Prime the Pen. 2) If you are sure insulin is coming out of the needle, push in the injection button more slowly to reduce the effort needed and maintain a constant pressure until the injection button is completely pushed in.

For additional information call,
1-800-LILLY-RX (1-800-545-5979)

Revised XX, 2004

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

PA 9115 FSAMP

Humalog® Mix75/25™ Pen
5 x 3 mL
100 units per mL
HP8794
75% insulin lispro protamine suspension
25% insulin lispro injection (rDNA origin)
disposable insulin delivery device
U-100

Lilly

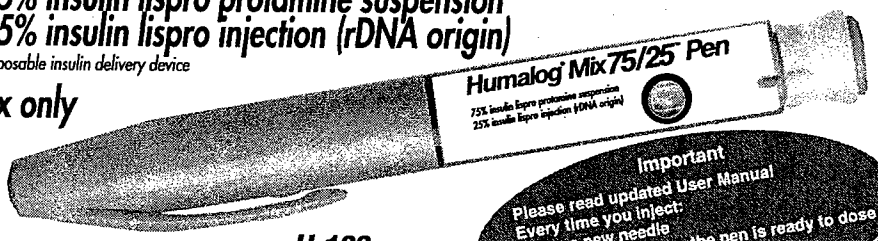
NDC 0002-8794-59
5 x 3 mL
HP8794
100 units per mL

Humalog® Mix75/25™ Pen

75% insulin lispro protamine suspension
25% insulin lispro injection (rDNA origin)

disposable insulin delivery device

Rx only



U-100

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

Important
Please read updated User Manual
Every time you inject:
✓ Use a new needle
✓ Prime to make sure the pen is ready to dose
✓ Make sure you got a full dose

Exp. Date / Control No.

Lilly

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

If the seal is broken before first use, contact pharmacist

3 0002-8794-59 3

Each mL contains 75 units insulin lispro protamine suspension; 25 units insulin lispro; protamine sulfate, 0.28 mg; glycerin, 16 mg; dibasic sodium phosphate, 3.78 mg; m-cresol, 1.76 mg; zinc oxide content adjusted to provide 0.025 mg zinc ion; phenol, 0.715 mg; and water for injection. Hydrochloric acid 10% and/or sodium hydroxide 10% may have been added to adjust pH.

IMPORTANT - SEE WARNINGS ON ACCOMPANYING INSERT

Keep in a cold place. Avoid freezing.
Shake carefully before using. See enclosed insert for proper technique.
Warning: Any change of insulin should be made cautiously and only under medical supervision.
For subcutaneous use only.
See accompanying insert for dosage.

If the seal is broken before first use, contact pharmacist

SH 8933 FSAMS

Lilly-France
116,5-27,5-186,5
Marbach Pr-Nr.
97 04 01 31

Lilly

Humalog® Mix75/25™ Pen
75% insulin lispro protamine suspension
25% insulin lispro injection (rDNA origin)
disposable insulin delivery device

U-100
5 x 3 mL
100 units per mL
HP8794

PA XXXX AMP

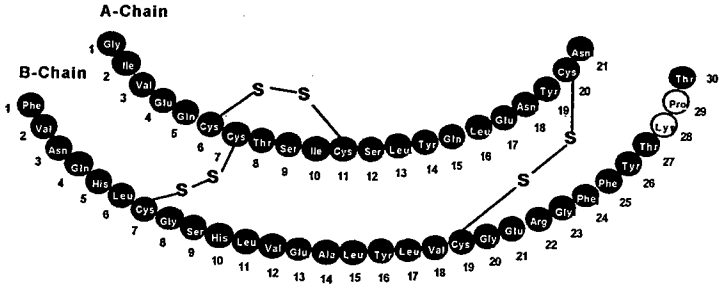
HUMALOG® Mix75/25™
75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN)

DESCRIPTION

Humalog® Mix75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for insulin lispro. Insulin lispro protamine suspension (NPL component) is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation.

Insulin lispro has the following primary structure:

Figure 1



Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

Humalog Mix75/25 vials, cartridges, and disposable insulin delivery devices contain a sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

Each milliliter of Humalog Mix75/25 injection contains insulin lispro 100 Units, 0.28 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg *m*-cresol, zinc oxide content adjusted to provide 0.025 mg zinc ion, 0.715 mg phenol, and water for injection. Humalog Mix75/25 has a pH of 7.0-7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may have been added to adjust pH.

CLINICAL PHARMACOLOGY

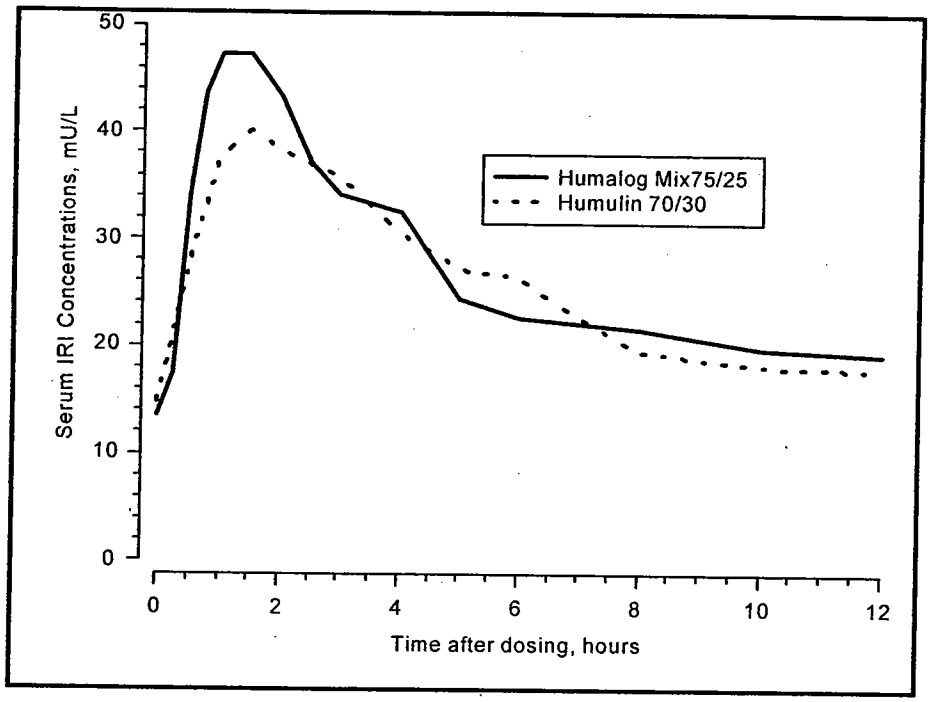
Antidiabetic Activity--The primary activity of insulin, including Humalog Mix75/25, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

Insulin lispro, the rapid-acting component of Humalog Mix75/25, has been shown to be equipotent to regular human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin, but its effect is more rapid and of shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared to Humulin 70/30 on a unit for unit basis.

Pharmacokinetics-

Absorption--Studies in nondiabetic subjects and patients with type 1 (insulin-dependent) diabetes demonstrated that Humalog®, the rapid-acting component of Humalog Mix75/25, is absorbed faster than regular human insulin (U100). In nondiabetic subjects given subcutaneous doses of Humalog ranging from 0.1-0.4 U/kg, peak serum concentrations were observed 30-90 minutes after dosing. When nondiabetic subjects received equivalent doses of regular human insulin, peak insulin concentrations occurred 50-120 minutes after dosing. Similar results were found in patients with type 1 diabetes.

Figure 2
Serum immunoreactive insulin (IRI) concentrations, after subcutaneous injection of Humalog Mix75/25 or Humulin 70/30 in healthy nondiabetic subjects



Humalog Mix75/25 has two phases of absorption. The early phase represents insulin lispro and its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin lispro protamine suspension. In 30 nondiabetic subjects given subcutaneous doses (0.3 U/kg) of Humalog Mix75/25, peak serum concentrations were observed 30 to 240 minutes (median, 60 minutes) after dosing (Figure 2). Identical results were found in patients with type 1 diabetes. The rapid absorption characteristics of Humalog are maintained with Humalog Mix75/25 (Figure 2).

Figure 2 represents serum insulin concentration versus time curves of Humalog Mix75/25 and Humulin® 70/30. Humalog Mix75/25 has a more rapid absorption than Humulin 70/30, which has been confirmed in patients with type 1 diabetes.

Distribution--radiolabeled distribution studies of Humalog Mix75/25 have not been conducted. However, the volume of distribution following injection of Humalog is identical to that of regular human insulin, with a range of 0.26-0.36 L/kg.

Metabolism--Human metabolism studies of Humalog Mix75/25 have not been conducted. Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of Humalog Mix75/25, is identical to that of regular human insulin.

Elimination--Humalog Mix75/25 has two absorption phases, a rapid and a prolonged phase, representative of the insulin lispro and insulin lispro protamine suspension components of the mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot be calculated after administration of Humalog Mix75/25 because of the prolonged insulin lispro protamine suspension absorption.

Pharmacodynamics--Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a more rapid onset of glucose-lowering activity, an earlier peak for glucose lowering, and a shorter duration of glucose-lowering activity than regular human insulin. The early onset of activity of Humalog Mix75/25 is directly related to the rapid absorption of Humalog. The time course of action of insulin and insulin analogs such as Humalog (and hence Humalog Mix75/25) may vary considerably in different individuals or within the same individual. The parameters of Humalog Mix75/25 activity (time of onset, peak time, and duration) as presented in Figures 2, 3, and 4 should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (*see* General *under* PRECAUTIONS).

In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and glucose-lowering activity of Humalog, Humalog Mix75/25, Humalog Mix50/50 and insulin lispro protamine suspension were compared (Figure 3). Graphs of mean glucose infusion rate versus time showed a distinct insulin activity profile for each formulation. The rapid onset of glucose-lowering activity characteristic of Humalog was maintained in Humalog Mix75/25.

In separate glucose clamp studies performed in nondiabetic subjects, glucodynamics of Humalog Mix75/25 and Humulin 70/30 were assessed and are presented in Figure 4. Humalog Mix75/25 has a duration of activity similar to that of Humulin 70/30.

Figure 3
Insulin activity after injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or insulin lispro protamine suspension (NPL component) in 30 nondiabetic subjects.

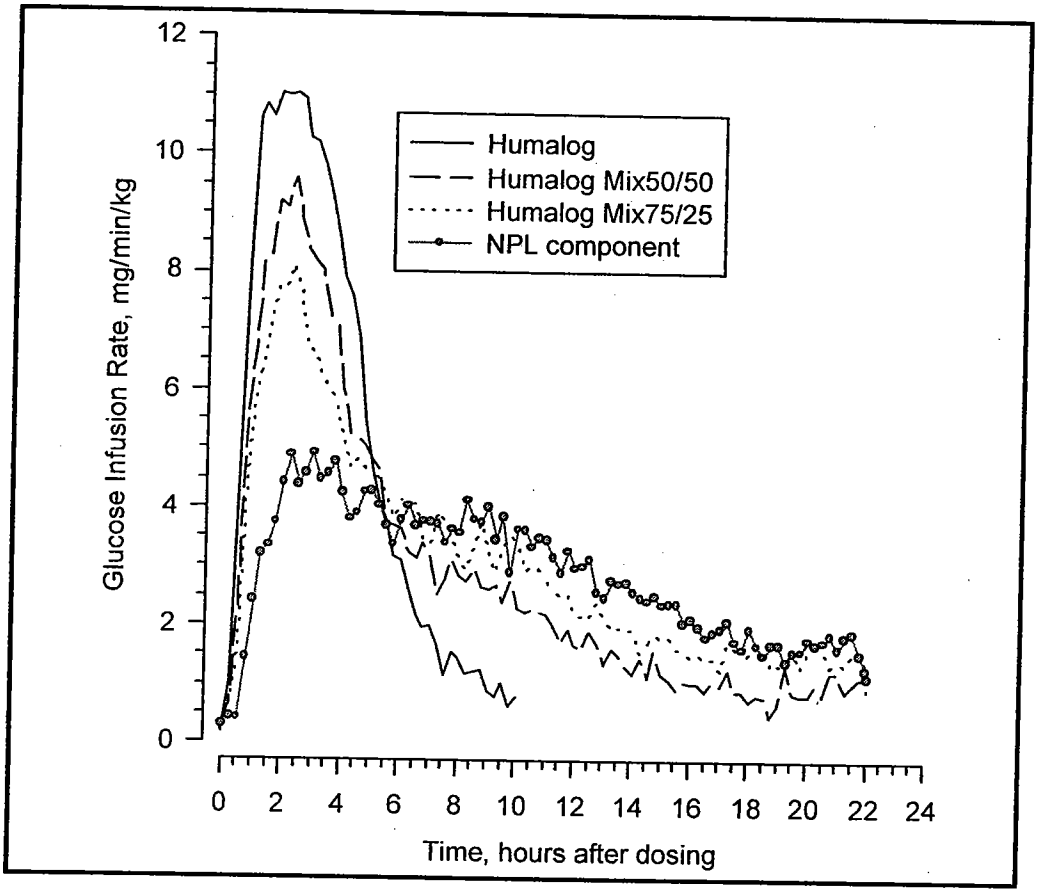
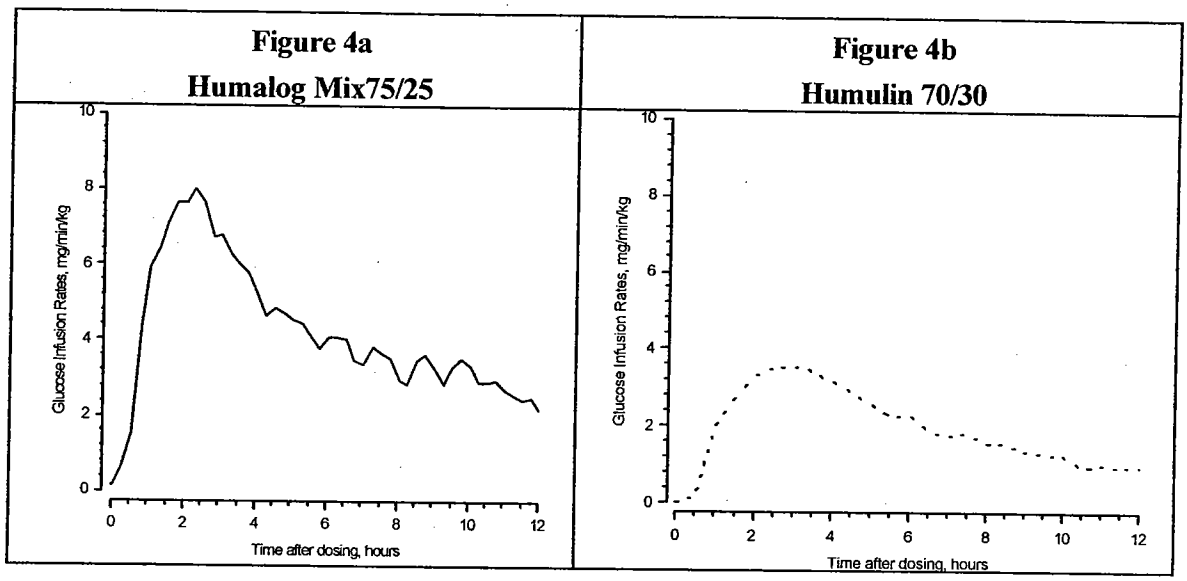


Figure 4
Insulin activity after injection of Humalog Mix75/25 and Humulin 70/30 in nondiabetic subjects.



Figures 3 and 4 represent insulin activity profiles as measured by glucose clamp studies in healthy nondiabetic subjects.

Figure 3 shows the time activity profiles of Humalog, Humalog Mix75/25, Humalog Mix50/50, and insulin lispro protamine suspension (NPL component).

Figure 4 is a comparison of the time activity profiles of Humalog Mix75/25 (Figure 4a) and of Humulin 70/30 (Figure 4b) from two different studies.

Special Populations--

Age and Gender--Information on the effect of age on the pharmacokinetics of Humalog Mix75/25 is unavailable. Pharmacokinetic and pharmacodynamic comparisons between men and women administered Humalog Mix75/25 showed no gender differences. In large Humalog clinical trials, subgroup analyses based upon age and gender demonstrated that differences between Humalog and regular human insulin in postprandial glucose parameters are maintained across sub-groups.

Smoking--The effect of smoking on the pharmacokinetics and glucodynamics of Humalog Mix75/25 has not been studied.

Pregnancy--The effect of pregnancy on the pharmacokinetics and glucodynamics of Humalog Mix75/25 has not been studied.

Obesity--The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of Humalog Mix75/25 has not been studied. In large clinical trials, which included patients with Body-Mass-Index up to and including 35 kg/m^2,

no consistent differences were observed between Humalog and Humulin R with respect to postprandial glucose parameters.

Renal Impairment--The effect of renal impairment on the pharmacokinetics and glucodynamics of Humalog Mix75/25 has not been studied. In a study of 25 patients with type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between Humalog and human regular insulin were generally maintained. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Careful glucose monitoring and dose reductions of insulin, including Humalog Mix75/25, may be necessary in patients with renal dysfunction.

Hepatic Impairment--Some studies with human insulin have shown increased circulating levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the pharmacokinetics and glucodynamics of Humalog Mix75/25 has not been studied. However, in a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the subcutaneous absorption or general disposition of Humalog when compared to patients with no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption and elimination when compared to regular human insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog Mix75/25, may be necessary in patients with hepatic dysfunction.

INDICATIONS AND USAGE

Humalog Mix75/25, a mixture of 75% insulin lispro protamine suspension and 25% insulin lispro, is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog Mix75/25 has a more rapid onset of glucose-lowering activity compared to Humulin 70/30 while having a similar duration of action. This profile is achieved by combining the rapid onset of Humalog with the intermediate action of insulin lispro protamine suspension.

CONTRAINDICATIONS

Humalog Mix75/25 is contraindicated during episodes of hypoglycemia and in patients sensitive to insulin lispro or any of the excipients contained in the formulation.

WARNINGS

Humalog differs from regular human insulin by its rapid onset of action as well as a shorter duration of activity. Therefore, the dose of Humalog Mix75/25 should be given within 15 minutes before a meal.

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog Mix75/25. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

PRECAUTIONS

General--Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog Mix75/25 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of action of Humalog Mix75/25 may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia--As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog Mix75/25. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment--As with other insulins, the requirements for Humalog Mix75/25 may be reduced in patients with renal impairment.

Hepatic Impairment--Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including Humalog Mix75/25, may be necessary.

Allergy--Local Allergy--As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy--Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Antibody Production--In clinical trials, antibodies that cross react with human insulin and insulin lispro were observed in both human insulin mixtures and insulin lispro mixtures treatment groups.

Information for Patients--Patients should be informed of the potential risks and advantages of Humalog Mix75/25 and alternative therapies. Patients should not mix Humalog Mix75/25 with any other insulin. They should also be informed about the

importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant.

Refer patients to the Information for the Patient insert for information on normal appearance, proper resuspension and injection techniques, timing of dosing (within 15 minutes before a meal), storing, and common adverse effects.

Laboratory Tests--As with all insulins, the therapeutic response to Humalog Mix75/25 should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

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.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility--Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog or Humalog Mix75/25. Insulin lispro was not mutagenic in a battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test). There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

Pregnancy--Teratogenic Effects--Pregnancy Category B--Reproduction studies with insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are, however, no adequate and well-controlled studies with Humalog or Humalog Mix75/25 in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers--It is unknown whether insulin lispro is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when Humalog Mix75/25 is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog Mix75/25 dose, meal plan, or both.

Pediatric Use--Safety and effectiveness of Humalog Mix75/25 in patients less than 18 years of age have not been established.

Geriatric Use--Clinical studies of Humalog Mix75/25 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger

patients. In general, dose selection for an elderly patient should take into consideration the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

ADVERSE REACTIONS

Clinical studies comparing Humalog Mix75/25 with human insulin mixtures did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole--allergic reactions (*see* PRECAUTIONS)

Skin and Appendages--injection site reaction, lipodystrophy, pruritus, rash

Other--hypoglycemia (*see* WARNINGS *and* PRECAUTIONS)

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

Table 1*
Summary of glucodynamic properties of insulin products (pooled cross-study comparison)

Insulin Products	Dose, U/kg	Time of peak activity, hours after dosing	Percent of total activity occurring in the first 4 hours
Humalog	0.3	2.4(0.8 – 4.3)	70% (49 – 89%)
Humulin R	0.32 (0.26 – 0.37)	4.4 (4.0 – 5.5)	54% (38 – 65%)
Humalog Mix 75/25	0.3	2.6 (1.0 – 6.5)	35% (21 – 56%)
Humulin 70/30	0.3	4.4 (1.5 - 16)	32% (14 – 60%)
Humalog Mix 50/50	0.3	2.3 (0.8 – 4.8)	45% (27 – 69%)
Humulin 50/50	0.3	3.3 (2.0 – 5.5)	44% (21 – 60%)
NPH	0.32 (0.27 – 0.40)	5.5 (3.5 – 9.5)	14% (3.0 – 48%)
NPL component	0.3	5.8 (1.3 – 18.3)	22% (6.3 – 40%)

*The information supplied in Table 1 indicates when peak insulin activity can be expected and the percent of the total insulin activity occurring during the first 4 hours. The information was derived from 3 separate glucose clamp studies in nondiabetic subjects. Values represent means, with ranges provided in parentheses.

Humalog Mix75/25 is intended only for subcutaneous administration. Humalog Mix75/25 should not be administered intravenously. Dosage regimens of Humalog Mix75/25 will vary among patients and should be determined by the health care professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Humalog has been shown to be equipotent to regular human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin, but its effect is more rapid and of shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared to Humulin 70/30 on a unit for unit basis. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

Humalog Mix75/25 starts lowering blood glucose more quickly than regular human insulin, allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast, mixtures containing regular human insulin should be given 30-60 minutes before a meal.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. As with all insulin preparations, the time course of action of Humalog Mix75/25 may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog Mix75/25 should be inspected visually before use. Humalog Mix75/25 should be used only if it appears uniformly cloudy after mixing. Humalog Mix75/25 should not be used after its expiration date.

HOW SUPPLIED

Humalog Mix75/25 vials are available in the following package size:
100 units per mL (U100)
10 mL vials
NDC 0002-7511-01 (VL-7511)

Humalog Mix75/25 cartridges are available in the following package size:
5 x 3 mL cartridges*
NDC 0002-7394-59 (VL-7394)

Humalog Mix75/25 Pen, a disposable insulin delivery device, is available in the following package size:
5 x 3 mL disposable insulin delivery devices
NDC 0002-8794-59 (HP-8794)

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*Cartridges are for use in Eli Lilly and Company's HumaPen and HumaPen®‡ Ergo, Becton Dickinson and Company's B-D Pen 3 ml, B-D®§ Pen Ultra, and Owen Mumford, Ltd.'s Autopen®‖ 3.0 mL insulin delivery devices.

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‡HumaPen® is a registered trademark of Eli Lilly and Company.
§B-D® is a registered trademark of Becton Dickinson and Company.
‖Autopen® is a registered trademark of Owen Mumford, Ltd.

Storage--Humalog Mix75/25 should be stored in a refrigerator (2° to 8°C [36° to 46°F]) before use, but not in the freezer. However, vials of Humalog Mix75/25 in use can be kept unrefrigerated at room temperature for up to 28 days, as long as they are kept as cool as possible and away from direct heat and light. Cartridges of Humalog Mix75/25 or Humalog

Mix75/25 Pens in use can be kept unrefrigerated at room temperature for up to 10 days, as long as they are kept as cool as possible and away from direct heat and light. Unrefrigerated vials, cartridges, and Pens must be used within the specified time periods or be discarded. Do not use Humalog Mix75/25 if it has been frozen.

Literature issued December, 1999
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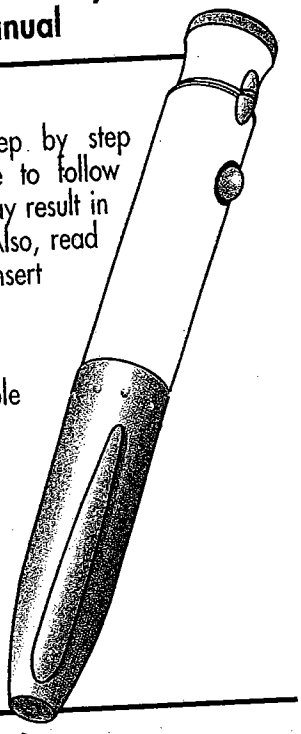
APPROVED

Lilly

FEB 8 2002

Disposable Insulin Delivery Device
User Manual



Instructions for Use

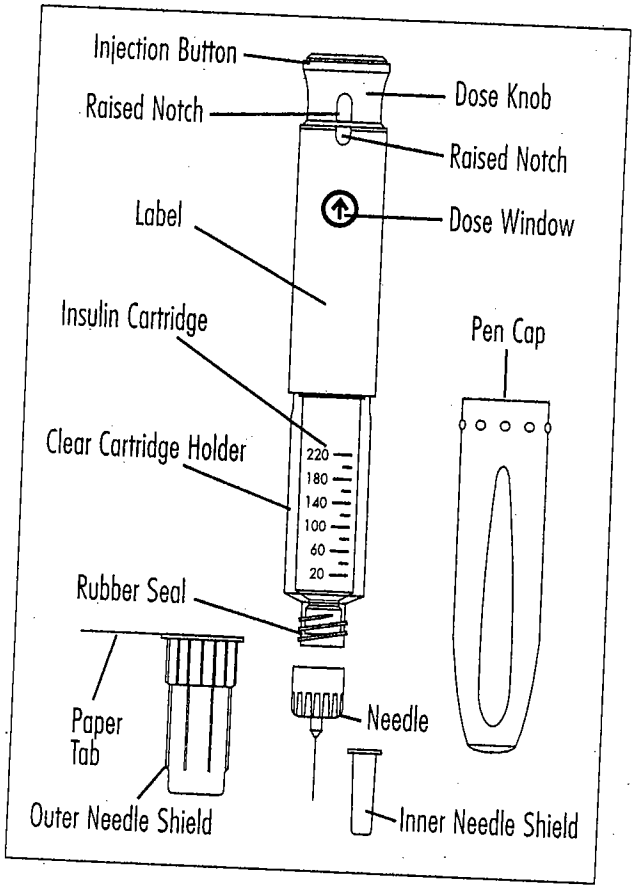
Read and follow these step by step instructions carefully. Failure to follow these instructions carefully may result in an inaccurate insulin dose. Also, read the *Information for the Patient* insert enclosed in your pen box.

Pen Features

- A multiple dose, disposable insulin delivery device ("insulin pen") containing 3 mL (300 units) of U-100 insulin
- Delivers up to 60 units per dose
- Doses can be dialed by single units

Table of Contents

Pen Parts



Important Notes

- **Please read these instructions carefully before using your Pen. Failure to follow these instructions carefully may result in an inaccurate dose.**
- Use a new needle for each injection.
- Be sure a needle is attached to the Pen before priming, setting (dialing) the dose and injecting your insulin.
- The numbers on the clear cartridge holder give an estimate of the amount of insulin remaining in the cartridge. Do not use these numbers for measuring an insulin dose.
- Do not share your Pen.
- Keep your Pen out of the reach of children.
- Pens not being used should be stored in a refrigerator but not in a freezer. Refer to the *Information for the Patient* insert for complete storage instructions.

Important Notes (Continued)

- Do not store your Pen with the needle attached. Doing so may allow insulin to leak from the Pen and air bubbles to form in the cartridge. Additionally, with suspension (cloudy) insulins, crystals may clog the needle.
- Always carry an extra Pen in case yours is lost or damaged.
- Dispose of empty Pens as instructed by your Health Care Professional and without the needle attached.
- This Pen is not recommended for use by blind or visually impaired persons without the assistance of a person trained in the proper use of the product.
- **Any changes in insulin should be made cautiously and only under medical supervision.**

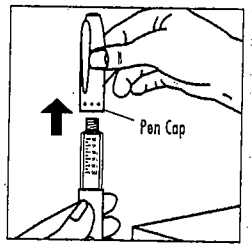
1. Preparing the Pen

1. Before proceeding, refer to the *Information for the Patient* insert for instructions on checking the appearance of your insulin.

2. Check the label on the Pen to be sure the Pen contains the type of insulin that has been prescribed for you.

3. Always wash your hands before preparing your Pen for use.

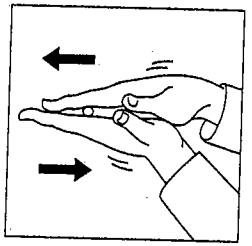
4. Pull the Pen cap to remove.



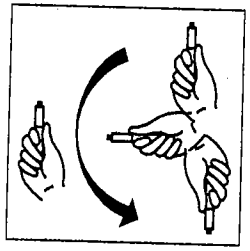
1. Preparing the Pen (Continued)

5. If your insulin is a suspension (cloudy):

   a. Roll the Pen back and forth 10 times then perform step b.

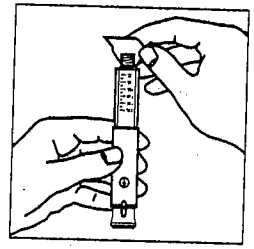


   b. Gently turn the Pen up and down 10 times until the insulin is evenly mixed.



Note: Suspension (cloudy) insulin cartridges contain a small bead to assist in mixing.

6. Use an alcohol swab to wipe the rubber seal on the end of the Pen.

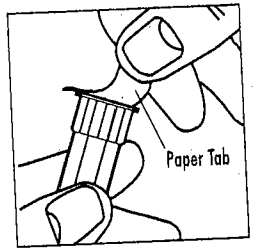


II. Attaching the Needle

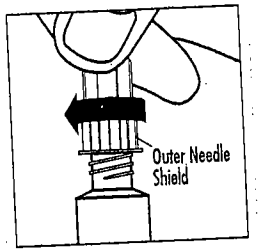
This device is suitable for use with Becton Dickinson and Company's insulin pen needles or their equivalent.

1. **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**

2. Remove the paper tab from the outer needle shield.

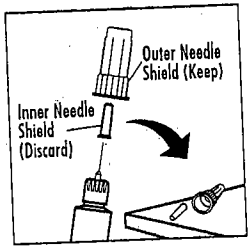


3. Attach the capped needle onto the end of the Pen by turning it clockwise until tight.



II. Attaching the Needle (Continued)

4. Hold the Pen with the needle pointing up and remove the **outer needle shield. Keep it to use during needle removal.**



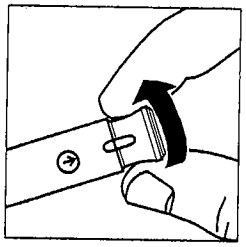
5. **Remove the inner needle shield and discard.**

III. Priming the Pen
(Checking Insulin Flow and Removing Air Bubbles)

- **Always use a new needle for each injection.**

Small air bubbles may collect in the insulin cartridge during normal use. Before each injection, carefully follow these instructions to make sure your Pen is properly primed and ready to deliver your insulin dose.*

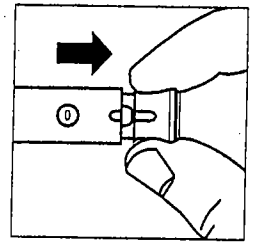
1. You cannot prime your Pen until you can see the arrow (→) in the dose window. If a number or a blank space is in the dose window, push in the injection button completely until a diamond (◆) or arrow (→) is seen. When diamonds (◆) can be seen in the dose window, turn the dose knob clockwise until the arrow (→) is seen and the notches on the Pen and dose knob are in line.



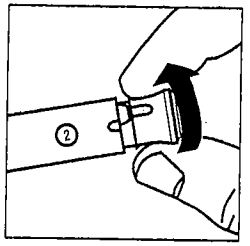
* See Page 16

III. Priming the Pen
(Continued)

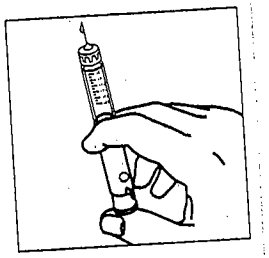
2. With the arrow in the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window.



3. Turn the dose knob clockwise until the number "2" is seen in the dose window.

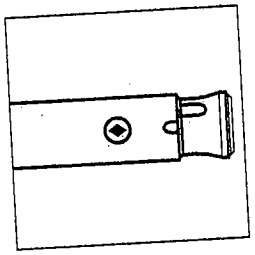


III. Priming the Pen (continued)



4. Hold your Pen with the needle pointing up. Tap the clear cartridge holder gently with your finger so any air bubbles collect near the top. Using your thumb, if possible, push in the injection button completely and maintain pressure until the insulin flow stops. You should see either a drop or a stream of insulin come out of the tip of the needle. If insulin does not come out of the tip of the needle, repeat steps 1 through 4. If after several attempts insulin does not come out of the tip of the needle, refer to the "Questions and Answers" section at the end of this manual.

III. Priming the Pen (continued)



5. At the completion of the priming step, a diamond (◆) must be seen in the dose window.

Note: A small air bubble may remain in the cartridge after the completion of the priming step. If you have properly primed the Pen, this small air bubble will not affect your insulin dose.

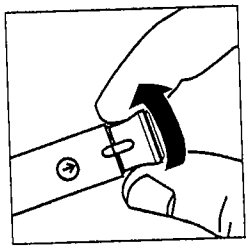
6. Now you are ready to set your dose. See next page.

IV. Setting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**
- **Caution: Do not push in the injection button while setting your dose. Failure to follow these instructions carefully may result in an inaccurate insulin dose.***

1. Pen has been primed and a diamond (◆) can be seen in the dose window.

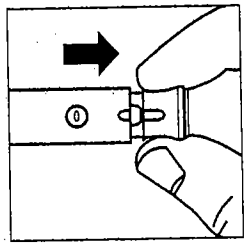
2. Turn the dose knob clockwise until the arrow (→) is seen in the dose window and the notches on the Pen and dose knob are in line.



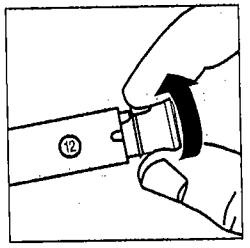
* See Page 16.

IV. Setting a Dose (Continued)

3. With the arrow (→) in the dose window, pull the dose knob out in the direction of the arrow until a "0" is seen in the dose window. A dose cannot be dialed until the dose knob is pulled out.



4. Turn the dose knob clockwise until your dose is seen in the dose window. If the dose you have dialed is too high, simply turn the dose knob backward until the correct dose is seen in the dose window.



5. If you cannot dial a full dose, see the "Questions and Answers" section at the end of this manual.

V. Injecting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**

- **Caution: Do not attempt to change the dose after you begin to push in the injection button. Failure to follow these instructions carefully may result in an inaccurate insulin dose.***

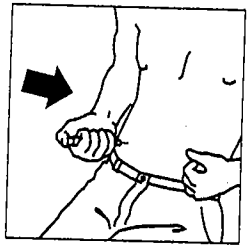
- **The effort needed to push in the injection button may increase while you are injecting your insulin dose. If you cannot completely push in the injection button, refer to the "Questions and Answers" section at the end of this manual.**

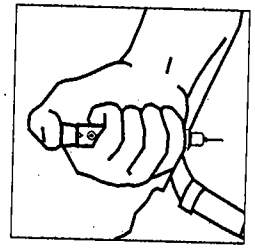
* If you have set (dialed) a dose and pushed in the injection button without the needle attached or if no insulin comes out of the needle, see the "Questions and Answers" section.

V. Injecting a Dose (Continued)

1. Wash hands. Prepare the skin and use the injection technique recommended by your Health Care Professional.

2. Inject the insulin by using your thumb, if possible, to completely push in the injection button. When the injection button has been completely pushed in (**a diamond (◆) or arrow (→) must be seen in the dose window to indicate that the injection button has been completely pushed in**), continue to hold it down and count **slowly** to 5. Remove the needle from the skin when you have finished counting.

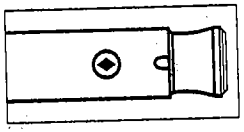




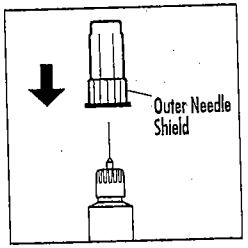
VI. Following an Injection

Do not store or dispose of the Pen with a needle attached. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.

1. Check that the injection button has been completely pushed in and you can see a diamond (◆) or arrow (→) in the dose window. If a diamond (◆) or arrow (→) cannot be seen in the dose window, your full dose has not been delivered. Contact your Health Care Professional immediately for additional instructions.

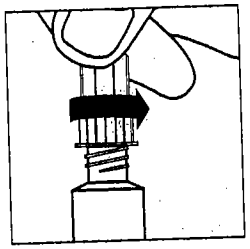


2. Carefully replace the **outer needle shield**.

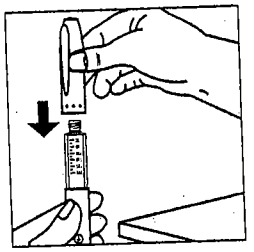


VI. Following an Injection (Continued)

3. Remove the capped needle by turning it counterclockwise and dispose of it as directed by your Health Care Professional.



4. Replace the cap on the Pen.



5. The Pen that you are currently using should be kept at a temperature below 86°F (30°C) and away from heat and light. It should be discarded according to the time specified in the *Information for the Patient* insert, even if it still contains insulin.

Questions and Answers

Problem	Action
Dose dialed and injection button pushed in without a needle attached.	To obtain an accurate dose you must: 1) Attach a new needle 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (◆) or arrow (→) is seen in the dose window. 3) Prime the Pen.
Insulin does not come out of the needle.	To obtain an accurate dose you must: 1) Attach a new needle 2) Push in the injection button completely (even if a "0" is seen in the window) until a diamond (◆) or arrow (→) is seen in the dose window. 3) Prime the Pen.

Questions and Answers (Continued)

Problem	Action
Wrong dose (too high or too low) dialed.	If you have not pushed in the injection button, simply turn the dose knob backward or forward to correct the dose.
Not sure how much insulin remains in the cartridge.	Hold the Pen with the needle end pointing down. The scale (20 units between marks) on the clear cartridge holder shows an estimate of the number of units remaining. **These numbers should not be used for measuring an insulin dose.**

Questions and Answers (Continued)

Problem	Action
Full dose cannot be dialed.	The Pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the Pen you will not be able to dial past 25. Do not attempt to dial past this point. (The insulin that remains is unusable and not part of the 300 units.) If a partial dose remains in the Pen you may either: 1) Give the partial dose and then give the remaining dose using a new Pen, or 2) Give the full dose with a new Pen.
A small amount of insulin remains in the cartridge but a dose cannot be dialed.	The Pen design prevents the cartridge from being completely emptied. The Pen has delivered 300 units of usable insulin.

Questions and Answers (Continued)

Problem	Action
Cannot completely push in the injection button when priming the Pen or injecting a dose.	1) Needle is not attached or is clogged. a. Attach a new needle b. Push in the injection button completely (even if a "0" is seen in the window) until a diamond (◆) or arrow (→) is seen in the dose window. c. Prime the Pen 2) If you are sure insulin is coming out of the needle, push in the injection button more slowly to reduce the effort needed and maintain a constant pressure until the injection button is completely pushed in.

For additional information call,
1-888-88-LILLY

Revised March 14, 2000

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

PA 9112 FSAMP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-017/s-002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP, HFD-510	21-017

3. NAME AND ADDRESS OF APPLICANT	4. SUPPLEMENT NUMBER, DATE
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285	SLR-002, 15-MAY-2000

5. NAME OF DRUG	6. NONPROPRIETARY NAME	8. AMENDMENTS/REPORT, DATE
Humalog Mix 75/25	75% insulin lispro protamine suspension and 25% insulin lispro injection	

7. SUPPLEMENT PROVIDES FOR:
Labeling changes to the disposable insulin delivery device User Manual.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND/NDA/DMF
Anti-hyperglycemic	Prescription	

12. DOSAGE FORM	13. POTENCY
Injectable	100 Units/ml

14. CHEMICAL NAME AND STRUCTURE
Insulin lispro; Lys(B28), Pro(B29) human insulin analogue (rDNA)

15. COMMENTS
See next page.

16. CONCLUSION AND RECOMMENDATIONS
Chemistry, manufacturing and controls information is satisfactory. Issue approval letter.

17. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Stephen Moore, Ph.D.	Chemistry Team Leader	13-MAR-01

DISTRIBUTION: ORIGINAL JACKET/CSO/REVIEWER/DIVISION FILE

R/D initialed by: File: N21017002.lp.doc

AP

15. COMMENTS (continued from page 1):

This Changes Being Effected supplement provides labeling changes to the disposable insulin delivery device User Manual. The changes are considered to be editorial. One noteworthy change is the deletion of the description of a click which is heard to indicate that the priming stroke is complete.

A telephone conversation was held between this reviewer and Dr. Jeff Winn of the firm on 31-July-2000 regarding the deletion of the written information about the click. Dr. Winn verified that the change was to the written description only, not a change to the pen itself. Dr. Winn explained that a click is not always heard when the priming stroke is complete, therefore, this could lead to confusion by patients.

Satisfactory.

/s/

Stephen Moore
3/13/01 02:54:31 PM
CHEMIST

CHEMIST'S REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP, HFD-510	18-781

3. NAME AND ADDRESS OF APPLICANT	4. SUPPLEMENT NUMBER, DATE
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 Attn: Gregory G. Enas, Ph.D., Dir., U.S. Regulatory Affairs 317-276-4038	18-781/S-057 (CBE-30) 19-717/S-032 " 20-563/S-027 " 21-017/S-002 " 21-018/S-001 " Dated 15-MAY-2000 (Recd. 17-MAY-2000)

5. NAME OF DRUG	6. NONPROPRIETARY NAME	8. AMENDMENTS/REPORT, DATE
Humulin N, Humulin 70/30, Humalog, Humalog Mix 75/25, Humalog Mix 50/50	Insulin drug products	

7. SUPPLEMENT PROVIDES FOR:
Labeling changes to the disposable insulin delivery device User Manual.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND/NDA/DMF
Insulin; treatment of diabetes	OTC	

12. DOSAGE FORM	13. POTENCY
Injectable suspension	100 Units/ml

14. CHEMICAL NAME AND STRUCTURE
Insulin human

15. COMMENTS
See next page.

16. CONCLUSION AND RECOMMENDATIONS
Chemistry, manufacturing and controls information is satisfactory. Issue approval letter.

17. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Stephen Moore, Ph.D.	Chemistry Team Leader	18-AUG-2000

DISTRIBUTION: ORIGINAL JACKET/CSO/REVIEWER/DIVISION FILE

R/D initialed by:
AP

File: N18781eg.ins

15. COMMENTS (continued from page 1):

This Changes Being Effected supplements provides for labeling changes to the disposable insulin delivery device User Manual. The labeling changes are considered to be minor. Noteworthy, the changes include the strike out of "A click can be felt or heard to indicate the injection

stroke is complete". I telephoned Dr. Jeff Winn of the firm on 7/31/2000 to find out if there had been any changes to the pen. Dr. Win verified that this was not a change to the pen itself. He further indicated that the click is not always heard, therefore it is being deleted to avoid patient confusion.

Satisfactory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-017/s-002

MEDICAL REVIEW

Division of Metabolic and Endocrine Drug Products
LABELING SUPPLEMENT REVIEW

Applications Reviewed:

Application	Submission Date	Supplement	Product Name
NDA 21-017	May 15, 2000	S-002	Humalog 75/25
NDA 21-018	May 15, 2000	S-001	Humalog 50/50

Background and Summary:

Both supplements provide for the changes in the User Manual for the Disposable Delivery Device. These supplements were reviewed for content upon receipt and it was determined that they did not qualify as "Special Supplements – Changes Being Effected," under 21 CFR 314.70 (c), as submitted by the sponsor.

The Disposable Delivery Device User Manual was initially approved for the Humulin N with NDA 18-780 / S -058 on August 6, 1998 (see labeling supplement amendment dated July 24, 1998 for approved version). The Humalog 75/25 and Humalog 50/50 product lines included cartridge formulations suitable for use with the Disposable Delivery Device when both NDAs were approved on December 22, 1999. The User Manual label is not product specific and is designed to be appropriate for use with all product lines in which the Disposable Delivery Device is acceptable.

Dr. Stephen Moore, chemistry team leader, completed reviews of the pending submissions, containing numerous clarifications to the User Manual label, on March 13, 2001 and recommended an approval action.

This labeling review confirms that the only changes made to the User Manual from its original approval under NDA 18-780 are those described by the sponsor in the pending submissions and reviewed by Dr. Moore. These changes appear to enhance comprehensibility of the labeling and substantive information regarding the device handling and injection procedures has not been omitted. No other changes are recommended.

There are no prior or subsequent labeling supplements pending for these products.

Conclusions:

An approval letter should be sent to the sponsor for each of the supplements. The currently approved labeling for the Disposable Insulin Delivery Device User Manual is as follows:
Indentifier "PA 9112 FSAMP"
Revision Date "March 14, 2000"

Susan Johnson
Labeling Reviewer, HFD-102
December 2, 2001

Kati Johnson
Supervisory Concurrence, HFD-510

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

/s/

Susan Johnson
12/3/01 06:28:28 PM
MEDICAL OFFICER

Kati Johnson
12/19/01 06:57:55 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-071/s-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 25 2000

NDA 21-017/S-002

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Gregory G. Enas, Ph.D.
Director, U.S. Regulatory Affairs

Dear Dr. Enas:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Humalog® Mix 75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)]

NDA Number: 21-017

Supplement Number: S-002

Date of Supplement: May 15, 2000

Date of Receipt: May 17, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on July 16, 2000, in accordance with 21 CFR 314.101(a).
All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

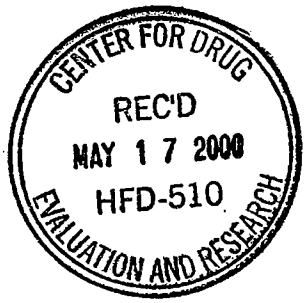
Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ORI
NDA NO 21017 SO
NDA SUPPL FOR SLR

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000



May 15, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic and
Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

CHANGES BEING EFFECTED

Re: NDA 20-563; Humalog® [25% insulin lispro injection (rDNA origin)]
NDA 21-017; Humalog® Mix 75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)]
NDA 21-018; Humalog® Mix 50/50™ [50% insulin lispro protamine suspension and 50% insulin lispro injection (rDNA origin)]
NDA 18-781; Humulin® N [human insulin isophane suspension (rDNA origin)]
NDA 19-717; Humulin® 70/30 [70% human insulin isophane suspension and 30% human insulin injection (rDNA origin)]

Eli Lilly and Company is herewith submitting labeling changes to the disposable insulin delivery device User Manual that is provided with the referenced drug products. The manual is not product specific. The changes are editorial in nature and meant to clarify the instructions provided in the manual and to prevent user misunderstanding and potential misuse. Therefore these changes are being submitted pursuant to 314.70(c), changes being effected.

At this time Lilly is submitting 1 copy of the document on 8 X 11 inch paper with deleted text being displayed as "large font" and deleted text being displayed as "strike-through" along with 20 copies of the final printed labeling, ten of which are mounted on heavy-weight paper.

Lilly thanks you for your continued support and assistance. Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 276-4038 if you require additional information or if there are any questions.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ FAX ☐ MEMO
CSO INITIALS DATE

Sincerely,

ELI LILLY AND COMPANY

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

Encl. PA 9112 FSAMP
cc: Janice Brown, PhD, HFD-510