CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020563/S003

Trade Name: HUMALOG

Generic Name: INSULIN LISPRO (rDNA ORIGIN) INJECTION

Sponsor: ELI LILLY AND COMPANY

Approval Date: 07/16/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020563/S003

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Bioequivalence Review(s)				
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020563/S003

APPROVAL LETTER

NDA 20-563/S-003

Eli Lilly and Company
Attention: Jennifer Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

JUL 16 1997

Dear Dr. Stotka:

Please refer to your supplemental new drug application dated November 12, 1996, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70(c) for Humalog [insulin lispro (rDNA origin) injection].

The supplemental application provides for the addition of Novo Nordisk A/S's NovoPen®, NovolinPen®, and NovoPen® 1.5 insulin delivery devices to the physician's package insert (circular PA 9121 FSAMP), patient's package insert (circular PA 9081 FSAMP), and the cartridge container label.

This addition was implemented on November 12, 1996, when the supplement was submitted.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on November 12, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

However, we request that the "Storage" subsection in the physician's package insert be moved from the DOSAGE AND ADMINISTRATION section to the HOW SUPPLIED section to be in accordance with 21 CFR 201.57(k)(4) at the next printing or in 6 months, whichever comes first, and report the change in the annual report.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be 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 20852-9787

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, please contact Julie Rhee, Project Manager, at (301) 443-3510.

Sincerely yours,

/S/ 7/17/97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-563
HFD-510/Div. files
HFD-510/CSO/J.Rhee
HFD-510/Koller/Fleming/Berlin/Moore/HRhee/Steigerwalt
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)

APPEARS THIS WAY
ON ORIGINAL

Drafted by: Rhee/June 11, 1997/ c:wpfiles/supplement/20563s03.ap
Initialed by:Galliers 6-24-97/Berlin 6-25-97/SMoore 6-25-97/Koller 6-25-97
final: JRhee 6-25-97 /S/ 6-25-97

SUPPLEMENT APPROVAL (AP S-003)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020563/S003

FINAL PRINTED LABELING

Labeling: SLR-003 ORIGINAL

NDA No: 20563 Rec'd. 11-13-96

Reviewed by: /S/ 6-3-97

APPROVED JUN 6 1997

IMPORTANT-SEE WARNINGS ON ACCOMPANYING CIRCULAR

Humalog insulin lispro injection (rDNA origin)
for information call 1-888-885-4559

To open, lift here and pull

Exp. Date / Control No.

5 Cartridges (1.5 mL)

Lilly

NDC 0002-7515-59
VL - 7515
100 units per mL

Humalog®

insulin lispro injection (rDNA origin)

CAUTION–Federal (USA) law prohibits dispensing without a prescription.

U-100

For use in Becton Dickinson and Company's B-D® Pen and B-D® Pen Ultra and Novo Nordisk A/S's NovoPen®, NovolinPen®, and NovoPen® 1.5 insulin delivery devices.

1.5 mL Lilly 5 x 1.5 mL cartridges 100 units per mL **U-100**

Humalog® insulin lispro injection (rDNA origin)

0 0002-7515-59 4

1.5 mL Lilly 5 x 1.5 mL cartridges 100 units per mL **U-100**

Humalog® insulin lispro injection (rDNA origin)

4

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APPEARS THIS WAY ON ORIGINAL

Humalog® *insulin lispro injection (rDNA origin)*

U-100

1.5 mL 5 x 1.5 mL cartridges
100 units per mL

Keep in a cold place. Avoid freezing.
Warning: Any change of insulin should be made cautiously and only under medical supervision.

For parenteral use.

See accompanying literature for dosage.

Each mL contains 100 Units of insulin lispro; glycerin, 16 mg; dibasic sodium phosphate, 1.88 mg; *m*-cresol, 3.15 mg; zinc oxide content adjusted to provide 0.0197 mg zinc ion; trace amounts of phenol, and water for injection. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

Neutral

Eli Lilly and Company
Indianapolis, Indiana 46285, U.S.A.
1-888-885-4559

SH 8611 FSAMS

APPEARS THIS WAY
ON ORIGINAL

INFORMATION FOR THE PATIENT

CARTRIDGE
HUMALOG®
INSULIN LISPRO INJECTION
(RECOMBINANT DNA ORIGIN)

For use in Becton Dickinson and Company's B-D®* Pen and B-D®* Pen Ultra and Novo Nordisk A/S's NovoPen®†, NovolinPen®† and NovoPen®† 1.5 insulin delivery devices.

WARNINGS

THIS LILLY HUMAN INSULIN ANALOG IS DIFFERENT FROM OTHER INSULINS BECAUSE IT HAS A NEW FORM THAT MAKES IT HAVE A VERY QUICK ONSET AND SHORTER DURATION OF ACTION. THE QUICK ONSET OF ACTION MEANS THAT YOU SHOULD TAKE YOUR DOSE OF HUMALOG® (INSULIN LISPRO, RECOMBINANT DNA ORIGIN) WITHIN 15 MINUTES BEFORE YOU EAT. THE SHORT DURATION OF ACTION OF HUMALOG MEANS THAT YOU ALSO NEED TO USE LONGER-ACTING INSULINS TO GIVE THE BEST GLUCOSE CONTROL.

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

PATIENTS TAKING HUMALOG 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 INSULIN DELIVERY DEVICE ("INSULIN PEN") MANUFACTURER'S INSTRUCTIONS AND THIS PATIENT INFORMATION BEFORE USING THIS PRODUCT IN AN INSULIN PEN. (*see* INSTRUCTIONS FOR 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.

Proper control of your diabetes requires close and constant cooperation with your doctor. In spite of diabetes, you can lead an active, healthy, and useful life if you eat a balanced diet daily, exercise regularly, and take your insulin injections as prescribed.

You have been instructed to test your blood and/or your urine regularly for glucose. If your blood tests consistently show above- or below-normal glucose levels or your urine tests consistently show the presence of glucose, your diabetes is not properly controlled and you must let your doctor know.

Always keep an extra supply of Humalog as well as a spare syringe and needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

HUMALOG

Description

Humalog 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 consists of zinc-insulin lispro crystals dissolved in a clear fluid. Humalog is a sterile solution and is for subcutaneous injection. It should not be used intramuscularly. The concentration of Humalog is 100 units/mL (U-100). Humalog starts lowering blood glucose more quickly and has a shorter duration of action compared to regular human insulin. This means that your dose of Humalog should be given within 15 minutes before a meal (regular insulin works best when given 30-60 minutes before a meal). The short duration of action of Humalog means that you need to use longer-acting insulins to give the best glucose control. The time course of Humalog action, like that of

DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION.

Cartridges of Humalog, 1.5 mL, are available in boxes of 5. Humalog cartridges are for use in Becton Dickinson and Company's B-D® Pen and B-D® Pen Ultra and Novo Nordisk A/S's NovoPen®, NovolinPen®, and NovoPen® 1.5 insulin delivery devices. The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge to be reused.

Always examine the appearance of a cartridge of Humalog before administering a dose. Humalog is a clear and colorless liquid with a water-like appearance and consistency. Do not use if it appears cloudy, thickened, or slightly colored, or if solid particles are visible. Always check the appearance of the cartridge of Humalog before using, and if you note anything unusual in its appearance or notice your insulin requirements changing markedly, consult your doctor.

Storage

Humalog cartridges should be stored in a refrigerator but not in the freezer. The insulin pen and cartridge of Humalog that you are currently using should not be refrigerated but should be kept as cool as possible (below 86°F [30°C]) and away from direct heat and light. Do not use Humalog if it has been frozen. Unrefrigerated cartridges must be discarded **after 28 days,** even if they still contain Humalog. Do not use a cartridge of Humalog after the expiration date stamped on the label.

INSTRUCTIONS FOR USE

Pens for insulin delivery differ in their operation. It is important to read, understand, and follow the instructions for use of the particular insulin pen you are using.

NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES

Preparing a Cartridge of Humalog for Insertion in an Insulin Pen

1. Wash your hands.
2. Inspect the Humalog in the cartridge. It should look clear and colorless. Do not use Humalog if it appears cloudy, thickened, or slightly colored, or if solid particles are visible.
3. Follow the insulin pen manufacturer's directions carefully for loading the cartridge into the insulin pen.

Injecting the Dose

1. Wash your hands.
2. Use an alcohol swab to wipe the exposed rubber surface on the metal cap end of the cartridge.
3. Inspect the Humalog in the cartridge. It should look clear and colorless. Do not use Humalog if it appears cloudy, thickened, or slightly colored or if solid particles are visible.
4. Follow the insulin pen manufacturer's directions for attaching and changing the needle.
5. Hold the insulin pen with needle pointing straight up. If there are large bubbles, tap the side of the insulin pen until they float to the top. Remove the bubbles and the air in the needle by setting the insulin pen to a 2-unit dose and depressing the plunger. Repeat this step if necessary until a drop of Humalog appears at the end of the needle. Set the insulin pen to the correct dose.
6. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the previous injection site.
7. Cleanse the skin with alcohol where the injection is to be made.
8. With one hand, stabilize the skin by spreading it or pinching up a large area.
9. Insert the needle as instructed by your doctor.
10. To inject Humalog, follow the insulin pen manufacturer's instructions.
11. Pull the needle out and apply gentle pressure over the injection site for several seconds.
12. Immediately after an injection, remove the needle from the insulin pen. This will guard against contamination and prevent leakage, reentry of air, and potential needle clogs. **Dispose of the needle in a responsible manner. Do not reuse needle.**
13. Once the cartridge is in use, do not continue to use it if the leading edge of the plunger is beyond the black band on the cartridge. If a dose is started when the leading edge of the plunger is beyond the black band, an appropriate dose may not be delivered. Use the gauge on the side of the cartridge to help you judge how much Humalog remains. The distance between each mark is about 10 units.

Injection

Once you have chosen an injection site, cleanse the skin with alcohol where the injection is to be made. Stabilize the skin by spreading it or pinching up a large area. Insert the needle as instructed by your doctor. Push the plunger in as far as it will go. Pull the needle out and apply gentle pressure over the injection site for several

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Identification

Cartridges of insulin lispro, manufactured by Eli Lilly and Company, have the trademark Humalog. Your doctor has prescribed the type of insulin that he/she believes is best for you.

NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES

Preparing a Cartridge of Humalog for Insertion in an Insulin Pen

1. Wash your hands.
2. Inspect the Humalog in the cartridge. It should look clear and colorless. Do not use Humalog if it appears cloudy, thickened, or slightly colored, or if solid particles are visible.
3. Follow the insulin pen manufacturer's directions carefully for loading the cartridge into the insulin pen.

Injecting the Dose

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8. With one hand, stabilize the skin by spreading it or pinching up a large area.
9. Insert the needle as instructed by your doctor.
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11. Pull the needle out and apply gentle pressure over the injection site for several seconds.
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Injection

Once you have chosen an injection site, cleanse the skin with alcohol where the injection is to be made. Stabilize the skin by spreading it or pinching up a large area. Insert the needle as instructed by your doctor. Push the plunger in as far as it will go. Pull the needle out and apply gentle pressure over the injection site for several seconds. To avoid tissue damage, give the next injection at a site at least 1/2" from the previous injection site. The usual sites of injection are abdomen, thighs, and arms.

After the injection

Immediately after an injection, remove the needle from the insulin pen. Doing so will guard against contamination and prevent leakage of Humalog, reentry of air, and needle clogs. Do not reuse needles and dispose of them in a responsible manner.

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 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 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/urine 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 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 hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, alcohol, and certain antidepressants. Your health care professional is aware of 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 dose, especially if the exercise involves the area of 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 (Insulin Reaction)

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 hypoglycemics, 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 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 Acidosis

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 insulin-dependent diabetes, prolonged hyperglycemia can result in diabetic acidosis. The first symptoms of diabetic acidosis 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 acidosis, urine tests show large amounts of glucose and acetone. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or diabetic acidosis can lead to nausea, vomiting, 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 national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, National Service Center, 1660 Duke Street, Alexandria, Virginia 22314, 1-800-DIABETES (1-800-342-2383). Another publication, **DIABETES COUNTDOWN**, is available from the Juvenile Diabetes Foundation International (JDF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873).

Additional information about Humalog can be obtained by calling 1-888-88-LILLY (1-888-885-4559).

Literature revised September 26, 1996

ELI LILLY AND COMPANY • Indianapolis, IN 46285, USA

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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 hypoglycemics, 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
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- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
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- 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,

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.

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ELI LILLY AND COMPANY • Indianapolis, IN 46285, USA

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* B-D is a trademark of Becton Dickinson and Company

† NovolinPen, NovoPen, and NovoPen 1.5 are trademarks of Novo Nordisk A/S.

PA 9081 FSAMP

APPEARS THIS WAY
ON ORIGINAL

HUMALOG®

INSULIN LISPRO INJECTION

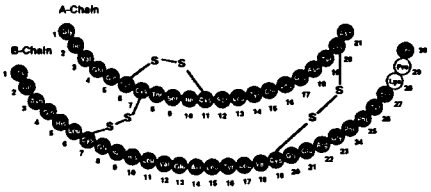
(rDNA ORIGIN)

DESCRIPTION

Humalog® (insulin lispro, rDNA origin) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. Chemically, it 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. Humalog 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.

Humalog has the following primary structure:

Figure 1



Humalog 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.

The vials and cartridges contain a sterile solution of Humalog for use as an injection. Humalog injection consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid.

Each milliliter of Humalog injection contains insulin lispro 100 Units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg *m*-cresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and water for injection. Insulin lispro has a pH of 7.0-7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

CLINICAL PHARMACOLOGY

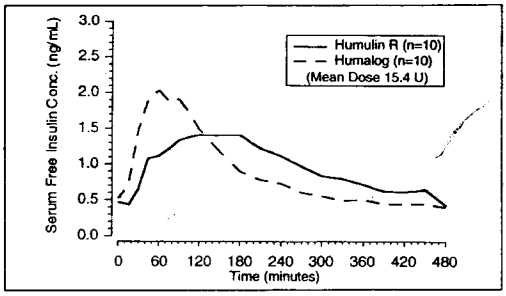
Antidiabetic Activity—The primary activity of insulin, including Humalog, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of 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.

Humalog has been shown to be equipotent to human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of human regular insulin, but its effect is more rapid and of shorter duration. The glucose-lowering activity of Humalog and human regular insulin is comparable when administered to normal volunteers by the intravenous route.

Pharmacokinetics—

Absorption and Bioavailability—Humalog is as bioavailable as human regular insulin, with absolute bioavailability ranging between 55%-77% with doses between 0.1-0.2 U/kg, inclusive. Studies in normal volunteers and patients with type I (insulin-dependent) diabetes demonstrated that Humalog is absorbed faster than human regular insulin (U100) (Figure 2). In normal volunteers given subcutaneous doses of Humalog ranging from 0.1-0.4 U/kg, peak serum levels were seen 30-90 minutes after dosing. When normal volunteers received equivalent doses of human regular insulin, peak insulin doses occurred between 50-120 minutes after dosing. Similar results were seen in patients with type I diabetes. The pharmacokinetic profiles of Humalog and human regular insulin are comparable to one another when administered to normal volunteers by the intravenous route. Humalog was absorbed at a consistently faster rate than human regular insulin in healthy male volunteers given 0.2 U/kg human regular insulin or Humalog at abdominal, deltoid, or femoral sites, the three sites often used by patients with diabetes. After abdominal administration of Humalog, serum drug levels are higher and the duration of action is slightly shorter than after deltoid or thigh administration (*see* DOSAGE AND ADMINISTRATION section). Humalog has less intra- and inter-patient variability compared to human regular insulin.

Figure 2
Serum Humalog and Insulin levels after subcutaneous injection of human regular insulin or Humalog (0.2 U/kg) immediately before a high carbohydrate meal in 10 patients with Type I diabetes.*



*Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

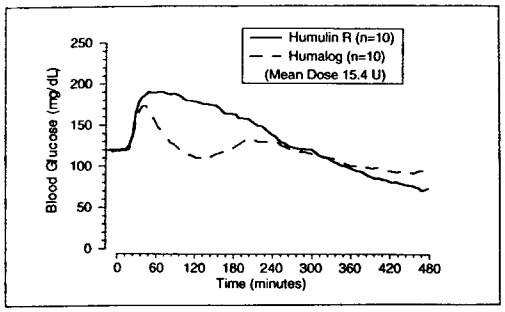
Distribution—The volume of distribution for Humalog is identical to that of human regular insulin, with a range of 0.26-0.36 L/kg.

Metabolism—Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of Humalog is identical to that of human regular insulin.

Elimination—When Humalog is given subcutaneously, its $t_{1/2}$ is shorter than that of human regular insulin (1 vs 1.5 hours, respectively). When given intravenously, Humalog and human regular insulin show identical dose-dependent elimination, with a $t_{1/2}$ of 26 and 52 minutes at 0.1 U/kg and 0.2 U/kg, respectively.

Pharmacodynamics—Studies in normal volunteers and patients with diabetes demonstrated

Figure 3
Blood glucose levels after subcutaneous injection of human regular insulin or Humalog (0.2 U/kg) immediately before a high carbohydrate meal in 10 patients with Type I diabetes.*



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In open-label, crossover studies of 1008 patients with type I diabetes and 722 patients with type II (non-insulin-dependent) diabetes, Humalog reduced postprandial glucose compared with human regular insulin (*see* Table). The clinical significance of improvement in postprandial hyperglycemia has not been established.

Comparison of Means of Glycemic Parameters at the End of Combined Treatment Periods. All Randomized Patients in Cross-over Studies (3 months for each treatment)

Type I, N=1008 Glycemic Parameter, (mmol/L)†	Humalog[a]	Humulin® R[a] *	p-value
Premeal Blood Glucose	11.64 ± 5.09	11.34 ± 4.96	.274
1-Hour Postprandial	12.91 ± 5.43	13.89 ± 5.37	<.001
2-Hour Postprandial	11.16 ± 5.30	12.87 ± 5.77	<.001
HbA1c (%)	8.24 ± 1.49	8.17 ± 1.46	.089
Type II, N=722 Glycemic Parameter, (mmol/L)†	**Humalog[a]**	**Humulin R[a]**	**p-value**
Premeal Blood Glucose	10.67 ± 3.77	10.17 ± 3.67	.002
1-Hour Postprandial	13.23 ± 4.43	13.89 ± 4.18	<.001
2-Hour Postprandial	12.08 ± 4.62	13.14 ± 4.48	<.001
HbA1c (%)	8.18 ± 1.30	8.18 ± 1.38	.924

[a]Mean ± Standard Deviation
*Humulin® (Regular insulin human injection, USP, [recombinant DNA origin])
†mg/dL = mmol/L x 18.0

In 12-month parallel studies of type I and type II patients, hemoglobin A_{1c} did not differ between patients treated with human regular insulin and those treated with Humalog.

While the overall rate of hypoglycemia did not differ between patients with type I and type II diabetes treated with Humalog compared with human regular insulin, patients with type I diabetes treated with Humalog had fewer hypoglycemic episodes between midnight and 6 a.m. The lower rate of hypoglycemia in the Humalog-treated group may have been related to higher nocturnal blood glucose levels, as reflected by a small increase in mean fasting blood glucose levels.

Special Populations –

Age and Gender—Information on the effect of age and gender on the pharmacokinetics of Humalog is unavailable. However, in large clinical trials, subgroup analysis based on age and gender did not indicate any difference in postprandial glucose parameters between Humalog and human regular insulin.

Smoking—The effect of smoking on the pharmacokinetics and glucodynamics of Humalog has not been studied.

Pregnancy—The effect of pregnancy on the pharmacokinetics and glucodynamics of Humalog has not been studied.

Obesity—The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of Humalog has not been studied. In large clinical trials, which included patients with Body-Mass-Index up to and including 35 kg/m², no consistent differences were seen between Humalog and Humulin R with respect to postprandial glucose parameters.

Renal Impairment—Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Information on the effect of renal impairment on the pharmacokinetics of Humalog is limited. Careful glucose monitoring and dose adjustments of insulin, including Humalog, may be necessary in patients with renal dysfunction.

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INDICATIONS AND USAGE

Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than human regular insulin. Therefore, Humalog should be used in regimens including a longer-acting insulin.

CONTRAINDICATIONS

Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or one of its excipients.

WARNINGS

This human insulin analog differs from human regular insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before the meal. Because of

1.88 mg dibasic sodium phosphate, 3.15 mg m-cresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and water for injection. Insulin lispro has a pH of 7.0-7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

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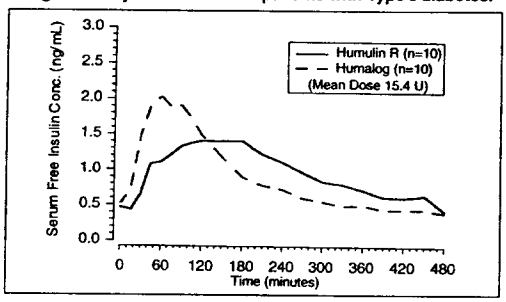

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Pharmacodynamics—Studies in normal volunteers and patients with diabetes demonstrated that Humalog has a more rapid onset of glucose-lowering activity, an earlier peak for glucose lowering, and a shorter duration of glucose-lowering activity than human regular insulin (Figure 3). The earlier onset of activity of Humalog is directly related to its more rapid rate of absorption. The time course of action of insulin and insulin analogs such as Humalog may vary considerably in different individuals or within the same individual. The parameters of Humalog activity (time of onset, peak time, and duration) as designated in Figure 3 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* PRECAUTIONS, Absorption and Bioavailability sub-section).

Glycemic Parameter, (mmol/L)†	Humalog[a]	Humulin® R[a] *	p-value
Premeal Blood Glucose	11.64 ± 5.09	11.34 ± 4.96	.274
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CONTRAINDICATIONS

Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or one of its excipients.

WARNINGS

This human insulin analog differs from human regular insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before the meal. Because of the short duration of action of Humalog, patients with type I diabetes also require a longer-acting insulin to maintain glucose control.

Hypoglycemia is the most common adverse effect of insulins, including Humalog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes[1].

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.

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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 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). 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 Humalog action 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. Rapid changes in serum glucose levels 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—Although there are no specific data in patients with diabetes, Humalog requirements may be reduced in the presence of renal impairment, similar to observations found with other insulins.

Hepatic Impairment—Although studies have not been performed in diabetes patients with hepatic disease, Humalog requirements may be reduced in the presence of impaired hepatic function, similar to observations found with other insulins.

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. In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving Humulin R (N=2969) and 30 patients receiving Humalog (N=2944) (p=.053). Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Antibody Production—In large clinical trials, antibodies that cross react with human insulin and insulin lispro were observed in both Humulin R- and Humalog–treatment groups. As expected, the largest increase in the antibody levels during the 12–month clinical trials was observed with patients new to insulin therapy.

Information for Patients—Patients should be informed of the potential risks and advantages of Humalog and alternative therapies. Patients 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 circular for information on proper injection technique, timing of Humalog dosing (≤ 15 minutes before a meal), storing and mixing insulin, and common adverse effects.

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

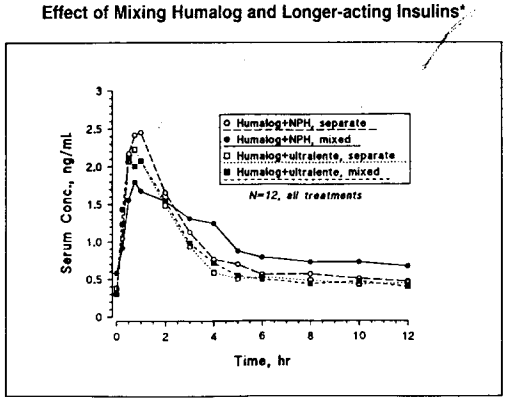
Drug Interactions—(*see* CLINICAL PHARMACOLOGY) Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy.

Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral hypoglycemic agents, salicylates, sulfa antibiotics, and 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.

Mixing of Insulins—Care should be taken when mixing all insulins as a change in peak action may occur. The American Diabetes Association warns in its Position Statement on Insulin Administration, "On mixing, physiochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately."[1] A decrease in the absorption rate, but not total bioavailability, was seen when Humalog was mixed with Humulin N. This decrease in absorption rate was not seen when Humalog was mixed with Humulin U (Figure 4). When Humalog is mixed with either Humulin U or Humulin N, the mixture should be given within 15 minutes before a meal.

Figure 4

Effect of Mixing Humalog and Longer-acting Insulins*



* Humalog and NPH or ultralente insulins were either injected from separate syringes or

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog. Humalog 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 Humalog-induced impairment of fertility.

Pregnancy–Teratogenic Effects–Pregnancy Category B—

Reproduction studies 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 Humalog. There are, however, no adequate and well-controlled studies 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.

Although there are no clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers—It is unknown whether Humalog 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 is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog dose, meal plan, or both.

Pediatric Use—Safety and effectiveness in patients less than 12 years of age have not been established.

ADVERSE REACTIONS

Clinical studies comparing Humalog with human regular insulin 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

Humalog is intended for subcutaneous administration. Dosage regimens of Humalog 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. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to human regular insulin (i.e., one unit of Humalog has the same glucose-lowering capability as one unit of human regular insulin), but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal insulin may be needed when a patient changes from other insulins to Humalog, particularly to prevent pre-meal hyperglycemia.

When used as a meal-time insulin, Humalog should be given within 15 minutes before a meal. Human regular insulin is best given 30-60 minutes before a meal. To achieve optimal glucose control, the amount of longer-acting insulin being given may need to be adjusted when using Humalog.

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. Humalog was absorbed at a consistently faster rate than human regular insulin in healthy male volunteers given 0.2 U/kg human regular insulin or Humalog at abdominal, deltoid, or femoral sites, the three sites often used by patients with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its rapid onset of action and has less variability in its onset of action among injection sites compared with human regular insulin (*see* PRECAUTIONS). After abdominal administration, Humalog concentrations are higher than those following deltoid or thigh injections. Also, the duration of action of Humalog is slightly shorter following abdominal injection, compared with deltoid and femoral injections. As with all insulin preparations, the time course of action of Humalog may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. If the solution is cloudy, contains particulate matter, is thickened, or is discolored, the contents must not be injected. Humalog should not be used after its expiration date.

Storage—Humalog should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the freezer. If refrigeration is impossible, the vial or cartridge of Humalog in use can be unrefrigerated for up to 28 days, as long as it is kept as cool as possible (not greater than 86°F [30°C]) and away from direct heat and light. Unrefrigerated vials and cartridges must be used within this time period or be discarded. Do not use Humalog if it has been frozen.

HOW SUPPLIED

Humalog (insulin lispro injection) is available in the following package sizes:

100 units per mL (U 100)

10 mL vials	NDC 0002-7510-01 (VL-7510)
5 - 1.5 mL cartridges*	NDC 0002-7515-59 (VL-7515)

*Cartridges are for use in Becton Dickinson and Company's B-D®† Pen and B-D®† Pen Ultra, and Novo Nordisk A/S's NovoPen®‡, NovolinPen®‡, and NovoPen®‡ 1.5 insulin delivery devices.

CAUTION—Federal (USA) law prohibits dispensing without prescription.

REFERENCES

1. American Diabetes Association: Clinical Practice Recommendations 1996, Insulin Administration. *Diabetes Care* 1996; 19(Supp 1):31-34.

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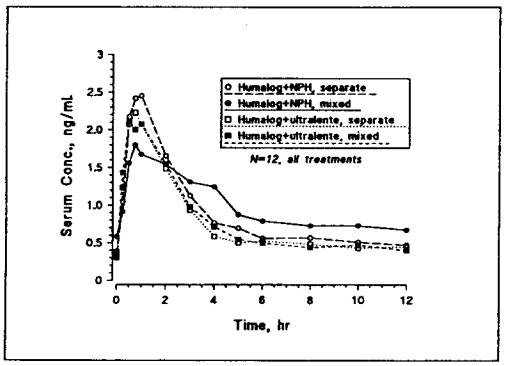
Laboratory Tests—As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

Drug Interactions—(*see* CLINICAL PHARMACOLOGY) 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 hypoglycemic agents, salicylates, sulfa antibiotics, and 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.

Mixing of Insulins—Care should be taken when mixing all insulins as a change in peak action may occur. The American Diabetes Association warns in its Position Statement on Insulin Administration, "On mixing, physiochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately."[1] A decrease in the absorption rate, but not total bioavailability, was seen when Humalog was mixed with Humulin N. This decrease in absorption rate was not seen when Humalog was mixed with Humulin U (Figure 4). When Humalog is mixed with either Humulin U or Humulin N, the mixture should be given within 15 minutes before a meal.

Figure 4
Effect of Mixing Humalog and Longer-acting Insulins*



* Humalog and NPH or ultralente insulins were either injected from separate syringes or mixed in the same syringe and injected together.

The effects of mixing Humalog with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (*see* WARNINGS).

If Humalog is mixed with a longer-acting insulin, Humalog should be drawn into the syringe first to prevent clouding of the Humalog by the longer-acting insulin. Injection should be made immediately after mixing. Mixtures should not be administered intravenously.

Clinical studies comparing Humalog with human regular insulin 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

Humalog is intended for subcutaneous administration. Dosage regimens of Humalog 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. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to human regular insulin (i.e., one unit of Humalog has the same glucose-lowering capability as one unit of human regular insulin), but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal insulin may be needed when a patient changes from other insulins to Humalog, particularly to prevent pre-meal hyperglycemia.

When used as a meal-time insulin, Humalog should be given within 15 minutes before a meal. Human regular insulin is best given 30-60 minutes before a meal. To achieve optimal glucose control, the amount of longer-acting insulin being given may need to be adjusted when using Humalog.

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. Humalog was absorbed at a consistently faster rate than human regular insulin in healthy male volunteers given 0.2 U/kg human regular insulin or Humalog at abdominal, deltoid, or femoral sites, the three sites often used by patients with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its rapid onset of action and has less variability in its onset of action among injection sites compared with human regular insulin (*see* PRECAUTIONS). After abdominal administration, Humalog concentrations are higher than those following deltoid or thigh injections. Also, the duration of action of Humalog is slightly shorter following abdominal injection, compared with deltoid and femoral injections. As with all insulin preparations, the time course of action of Humalog may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. If the solution is cloudy, contains particulate matter, is thickened, or is discolored, the contents must not be injected. Humalog should not be used after its expiration date.

Storage—Humalog should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the freezer. If refrigeration is impossible, the vial or cartridge of Humalog in use can be unrefrigerated for up to 28 days, as long as it is kept as cool as possible (not greater than 86°F [30°C]) and away from direct heat and light. Unrefrigerated vials and cartridges must be used within this time period or be discarded. Do not use Humalog if it has been frozen.

HOW SUPPLIED

Humalog (insulin lispro injection) is available in the following package sizes:

100 units per mL (U 100)	
10 mL vials	NDC 0002-7510-01 (VL-7510)
5 - 1.5 mL cartridges*	NDC 0002-7515-59 (VL-7515)

*Cartridges are for use in Becton Dickinson and Company's B-D®† Pen and B-D®† Pen Ultra, and Novo Nordisk A/S's NovoPen®‡, NovolinPen®‡, and NovoPen®‡ 1.5 insulin delivery devices.

CAUTION—Federal (USA) law prohibits dispensing without prescription.

REFERENCES

1. American Diabetes Association: Clinical Practice Recommendations 1996, Insulin Administration. *Diabetes Care*, 1996; 19(Supp 1):31-34.

† B-D is a trademark of Becton Dickinson and Company.
‡ NovolinPen, NovoPen, and NovoPen 1.5 are trademarks of Novo Nordisk A/S.

Literature revised September 26, 1996

ELI LILLY AND COMPANY • Indianapolis, IN 46285, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020563/S003

CHEMISTRY REVIEW(S)

ORIGINAL

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER MAY 12 1997
	DMEDP II, HFD-510	20-563

3. NAME AND ADDRESS OF APPLICANT	4. SUPPLEMENT NUMBER, DATE
Eli Lilly Research Labs., Inc. Lilly Corporate Center Indianapolis, IN 46285	SLR-003 11-12-96

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Humalog®	Lispro Insulin, rDNA origin	

8. SUPPLEMENT PROVIDES FOR

The addition of Novo Nordisk A/S's NovoPen®, NovolinPen®, and NovoPen® 1.5 insulin delivery devices to the labeling.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Insulin	RX	
12. DOSAGE FORM	13. POTENCY	
Injection	100 U/mL	

14. CHEMICAL NAME AND STRUCTURE

See Chemistry Review #1

15. COMMENTS

This application was submitted as CBE under 21 CFR 314.70(c). This is acceptable. The supplement provides example labels for the Humalog® package inserts containing references to the use of Novo Nordisk A/S's NovoPen®, NovolinPen®, and NovoPen 1.5® insulin delivery devices to both the physician's and patient's package inserts. The changes were made in accordance with approved-labeling changes made to the Sponsor's Humulin® drug products (reference: NDA 18-780, supplements dated 22 March, 1991 and 9 April, 1996).

16. CONCLUSION AND RECOMMENDATION

The sponsor had referenced the April 9, 1996 supplemental application to NDA 18-780 for supporting dose-accuracy data for use with Humalog® cartridges, 1.5 mL, in the above listed devices manufactured by Novo Nordisk A/S. The changes provided in this application accurately reflect those changes made and approved under NDA 18-780 for the Sponsor's Humulin® R drug product cartridge, 1.5 mL. Issue an approval letter.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
WILLIAM K. BERLIN	/S/	4-12-97

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

/S/ 5/12/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020563/S003

CORRESPONDENCE

NDA NO. [illegible] REF. NO. [illegible]

NDA SUPPL FOR SLR

ORIGINAL

Lilly

Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

November 12, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

**SPECIAL SUPPLEMENT--
CHANGES BEING EFFECTED**

Re: NDA 20-563--Humalog® (insulin lispro, rDNA origin)

Eli Lilly and Company is herewith amending the above referenced NDA in accordance with 21 C.F.R. 314.70(c).

Please refer to supplements made to NDA 18-780 Humulin® R (human insulin injection, rDNA origin) on March 22, 1991 and April 9, 1996. Please also refer to a telephone conversation between Dr. Stephen Moore (FDA) and Dr. Jeffrey Winn (Eli Lilly and Company) on June 4, 1996 in which Dr. Moore stated that it would be appropriate to submit the addition of Novo Nordisk A/S's NovoPen®, NovolinPen®, and NovoPen® 1.5 insulin delivery devices to the labeling of NDA 20-563 under 21 CFR 314.70(c). Dr. Moore indicated that NDA 18-780 should be referenced for dose accuracy studies.

Attached please find final printed labeling (FPL) for the aforementioned NDA 20-563.

Please call Dr. Kristi Kepler at (317) 277-7242 or my fax at (317) 276-1249 if there are any questions. Thank you for your continued cooperation and assistance.

CENTER FOR DRUG EVALUATION
RECD
NOV 13 1996
HFD

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs

Attachment

/S/

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO

/S/
CSO INITIALS DATE

/S/