A1.0 NL 4840 AMP

HUMALOG® Mix75/25™

75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN)

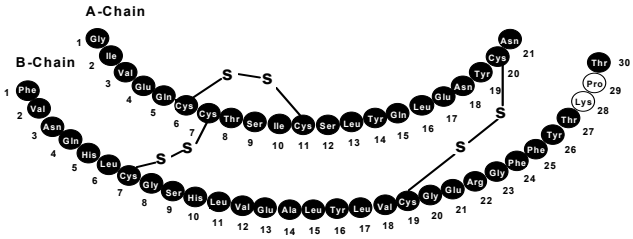
100 UNITS PER ML (U-100)

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 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.

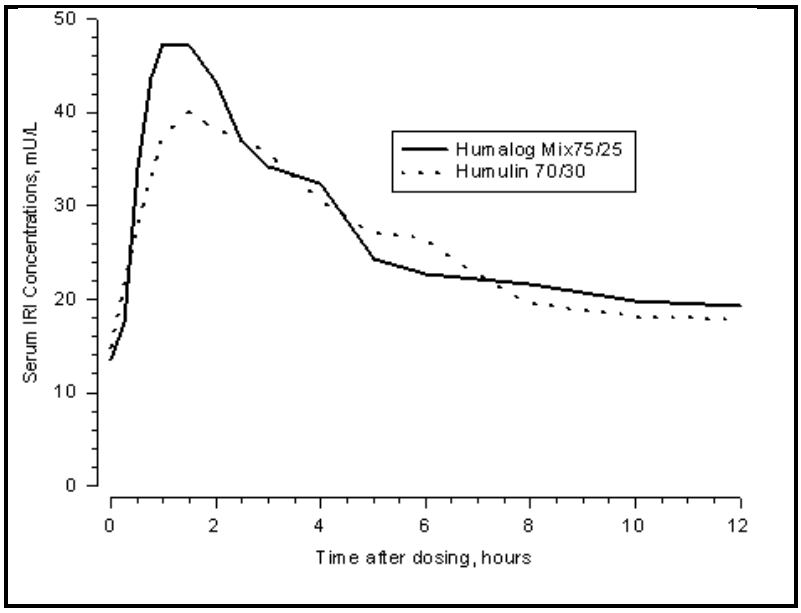
Insulin lispro, the rapid-acting component of Humalog Mix75/25, has been shown to be equipotent to regular human insulin on a molar basis. One unit of Humalog® has the same

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 (U-100). 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.

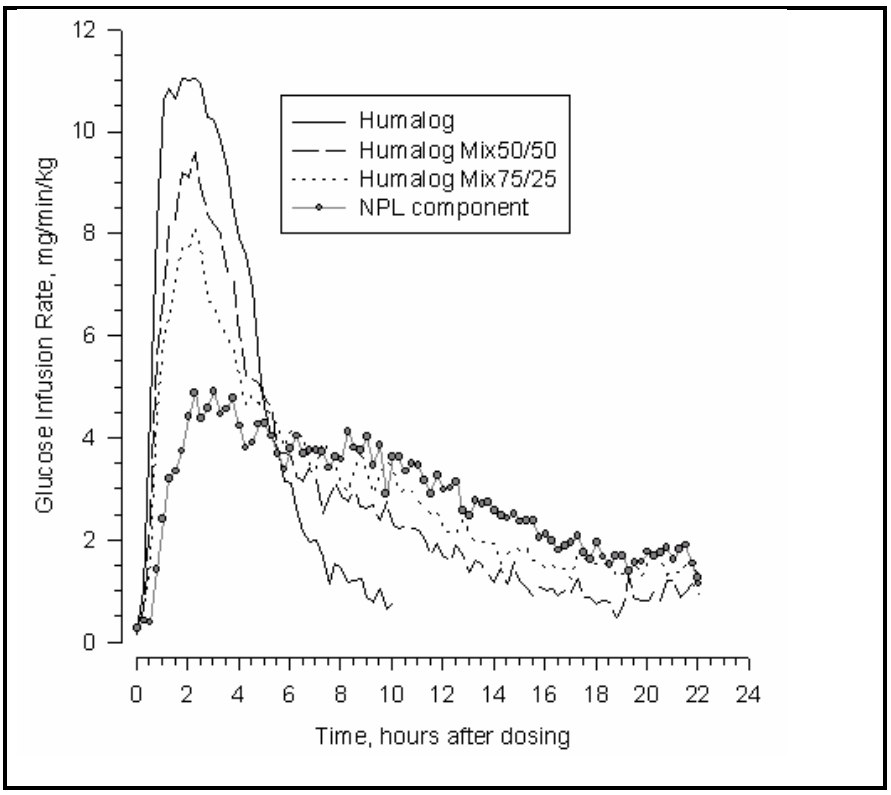
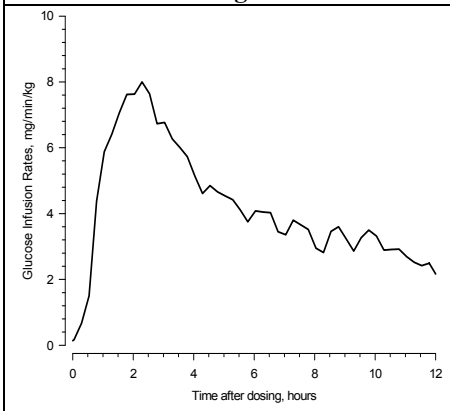
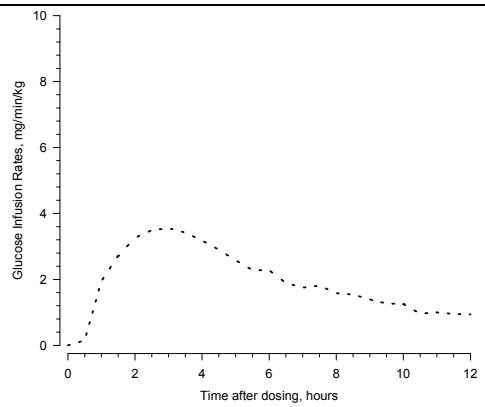


Figure 4
Insulin activity after injection of Humalog Mix75/25 and Humulin 70/30 in nondiabetic subjects.

Figure 4a Humalog Mix75/25	Figure 4b Humulin 70/30
	

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 the 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.

Use of the Humalog Mix75/25 Pen: Patients should read the "INFORMATION FOR THE PATIENT" insert and the "Disposable Insulin Delivery Device User Manual" before starting therapy with a Humalog Mix75/25 Pen and re-read them each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device (refer to "Disposable Insulin Delivery Device User Manual"), prime the Pen, and properly dispose of needles. Patients should be advised not to share their Pens with others.

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 Mix75/25	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 Mix50/50	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 (U-100)

10 mL vials

NDC 0002-7511-01 (VL-7511)

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)

Storage — Humalog Mix75/25 should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated (below 86°F [30°C]) vials must be used within 28 days or be discarded, even if they still contain Humalog Mix75/25. Unrefrigerated (below 86°F [30°C]) Pens must be used within 10 days or be discarded, even if they still contain Humalog Mix75/25. Protect Humalog Mix75/25 vials or Pens from direct heat and light. See table below:

	Not in-use (unopened) Room Temperature (below 86°F [30°C])	**Not in-use (unopened) Refrigerated**	**In-use (opened) Room Temperature (below 86°F [30°C])**
10 mLVial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen	10 days	Until expiration date	10 days. **Do not refrigerate.**

Literature issued XXXX 2003

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

A1.0 NL 4840 AMP PRINTED IN USA

Lilly's submission date: 2/25/04

A1.0 NL 4850 AMP

INFORMATION FOR THE PATIENT

VIAL

HUMALOG® Mix75/25™

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.

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 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 supply of Humalog Mix75/25 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 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, (rDNA origin). 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 injection (rDNA origin), manufactured 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.

Always check the carton and bottle labels of the Humalog Mix75/25 you receive from your pharmacy to make sure it is the same as that your doctor has prescribed.

Always examine the appearance of your bottle of Humalog Mix75/25 suspension before withdrawing each dose. A bottle of Humalog Mix75/25 must be carefully shaken or rotated several times to completely mix the insulin. Humalog Mix75/25 should look uniformly cloudy or milky after mixing. If not, repeat the above step until contents are mixed. Do not use if the insulin substance (the white material) remains at the bottom of the vial after mixing. Do not use a bottle of Humalog Mix75/25 if there are clumps in the insulin after mixing. Do not use a bottle of Humalog Mix75/25 if solid white particles stick to the bottom or wall of the bottle, giving it a frosted appearance. Always check the appearance of your bottle of 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

Humalog Mix75/25 should be stored in a refrigerator but not in the freezer. If refrigeration is not possible, the bottle of Humalog Mix75/25 that you are currently using can be kept unrefrigerated at room temperature (below 86°F [30°C]), **up to 28 days**, as long as it is kept as cool as possible and away from direct heat and light. Do not use Humalog Mix75/25 if it has been frozen. Do not use a bottle of Humalog Mix75/25 after the expiration date stamped on the label.

INJECTION PROCEDURES

NEVER SHARE NEEDLES AND SYRINGES

Correct Syringe Type

Doses of insulin are measured in **units**. U-100 insulin contains 100 units/mL (1 mL = 1 cc). With Humalog Mix75/25, it is important to use a syringe that is marked for U-100 insulin preparations.

Syringe Use

To help avoid contamination and possible infection, follow these instructions exactly.

Disposable plastic syringes and needles should be used only once and then discarded in a responsible manner.

Preparing the Dose

1. Wash your hands.
2. Carefully shake or rotate the insulin bottle several times to completely mix the insulin.
3. Inspect the insulin. Humalog Mix75/25 suspension should look uniformly cloudy or milky. Do not use it if you notice anything unusual in its appearance (*see* Identification above).
4. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper.
5. Wipe the top of the bottle with an alcohol swab.
6. Draw air into the syringe equal to your Humalog Mix75/25 dose. Put the needle through rubber top of the Humalog Mix75/25 bottle and inject the air into the bottle.
7. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.
8. Making sure the tip of the needle is in the Humalog Mix75/25, withdraw the correct dose into the syringe.
9. Before removing the needle from the bottle, check your syringe for air bubbles, which reduce the amount of Humalog Mix75/25. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
10. Remove the needle from the bottle and lay the syringe down so that the needle does not touch anything.

Injection Instructions

1. 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.
2. Cleanse the skin with alcohol where the injection is to be made.
3. With one hand, stabilize the skin by spreading it or pinching up a large area.
4. Insert the needle as instructed by your doctor.
5. Push the plunger in as far as it will go.
6. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.** 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 ~~h~~Health ~~c~~Care ~~p~~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 (~~Insulin Reaction~~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

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 diabetic ketoacidosis (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 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-

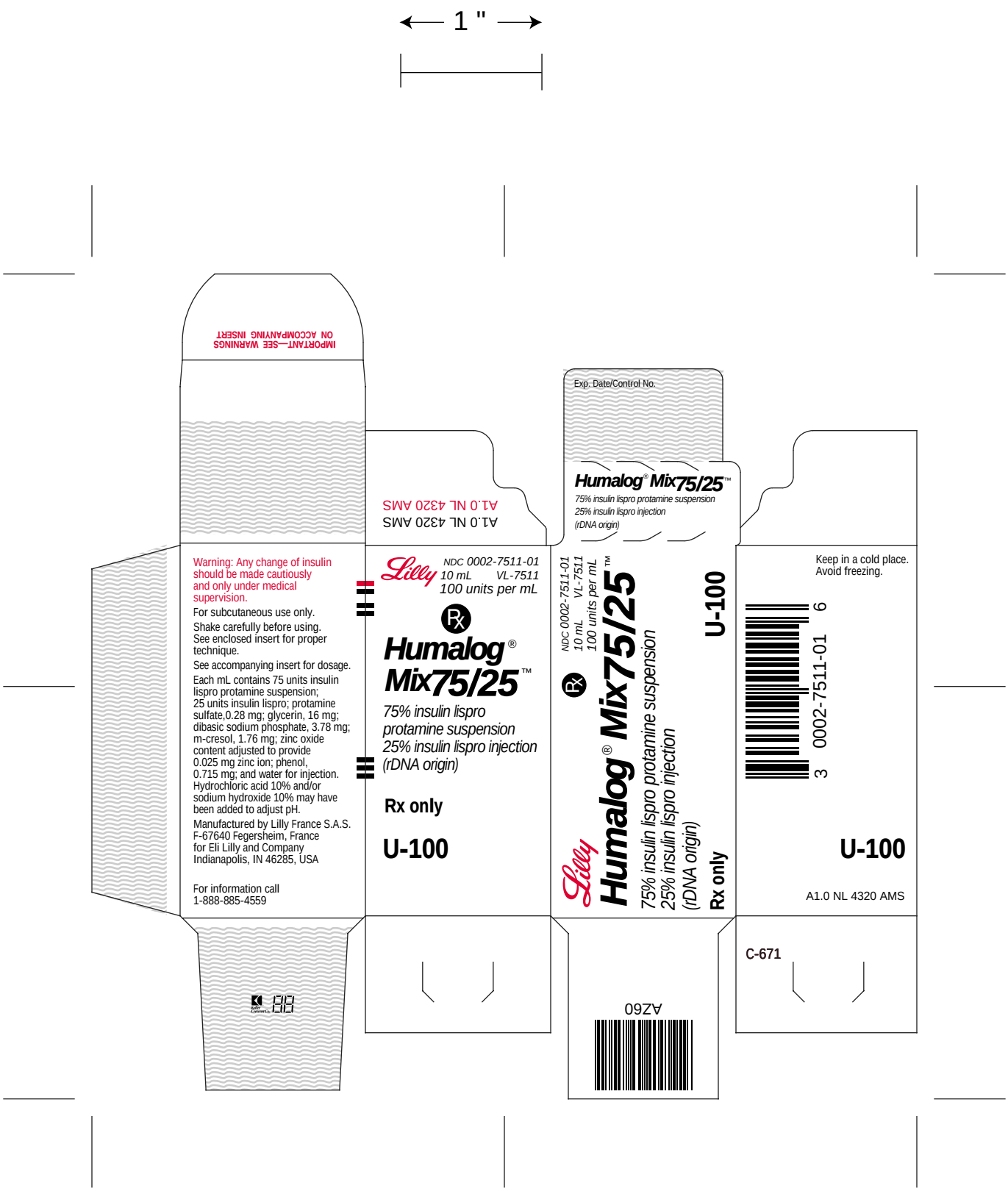
DIABETES (1-800-342-2383). Another publication, **DIABETES COUNTDOWN**, is available from the Juvenile Diabetes Foundation International (JDF), 120 Wall Street, 19th Floor, New York, New York 10005-4001, 1-800-JDF-CURE (1-800-533-2873).

Additional information about Humalog Mix75/25 can be obtained by calling 1-888-88-LILLY (1-888-885-4559) or consult the Eli Lilly and Company Internet Web Site at http://www.lilly.com/diabetes.

Literature issued XXX 2003

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

A1.0 NL 4850 AMP PRINTED IN USA



1 "