

**INFORMATION FOR THE PATIENT
3 ML PREFILLED INSULIN DELIVERY DEVICE**

**HUMULIN[®] N Pen
NPH
HUMAN INSULIN
(rDNA ORIGIN) ISOPHANE SUSPENSION
100 UNITS PER ML (U-100)**

WARNINGS

THIS LILLY HUMAN INSULIN PRODUCT DIFFERS FROM ANIMAL-SOURCE INSULINS BECAUSE IT IS STRUCTURALLY IDENTICAL TO THE INSULIN PRODUCED BY YOUR BODY'S PANCREAS AND BECAUSE OF ITS UNIQUE MANUFACTURING PROCESS.

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

SOME PATIENTS TAKING HUMULIN[®] (HUMAN INSULIN, rDNA ORIGIN) 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 USER MANUAL AND THIS "INFORMATION FOR THE PATIENT" INSERT BEFORE USING THIS PRODUCT.

THE PEN MUST BE PRIMED TO A STREAM OF INSULIN (NOT JUST A FEW DROPS) BEFORE EACH INJECTION TO MAKE SURE THE PEN IS READY TO DOSE. YOU MAY NEED TO PRIME A NEW PEN UP TO SIX TIMES BEFORE A STREAM OF INSULIN APPEARS.

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

DIABETES

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

To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near-normal level. You have been instructed to test your blood and/or your 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 or your hemoglobin A_{1c} (HbA_{1c}) is more than 7%, you should talk to your doctor. A change in your diabetes therapy may be needed. If your blood tests consistently show below-normal 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 by your doctor.

Always keep an extra supply of insulin 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.

NPH HUMAN INSULIN

Description

Humulin is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce human insulin. Humulin N [Human insulin (rDNA origin) isophane suspension] is a crystalline suspension of human insulin with protamine and zinc providing an intermediate-acting insulin with a slower onset of action and a longer duration of activity (up to 24 hours) than that of Regular human insulin. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of Humulin N is dependent on dose, site of injection, blood supply, temperature, and physical activity. Humulin N is a sterile suspension and is for subcutaneous injection only. It should not be used intravenously or intramuscularly. The concentration of Humulin N is 100 units/mL (U-100).

Identification

Human insulin from Eli Lilly and Company has the trademark Humulin. 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.

The Humulin N Pen is available in boxes of 5 prefilled insulin delivery devices ("insulin Pens"). The Humulin N Pen is not designed to allow any other insulin to be mixed in its cartridge, or for the cartridge to be removed.

Always check the carton and the Pen label for the name and letter designation of the insulin you receive from your pharmacy to make sure it is the same as prescribed by your doctor.

Always check the appearance of Humulin N suspension in your insulin Pen before using. A cartridge of Humulin N contains a small glass bead to assist in mixing. Roll the Pen back and forth between the palms 10 times (*see* Figure 1). Gently turn the Pen up and down 10 times until the insulin is evenly mixed (*see* Figure 2). If not evenly mixed, repeat the above steps until contents are mixed. Pens containing Humulin N suspension should be examined frequently.

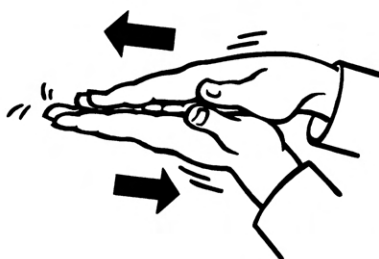


Figure 1.

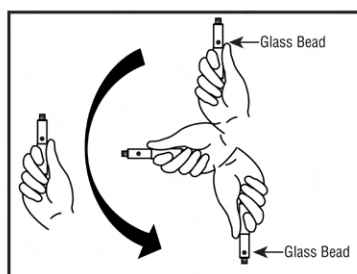


Figure 2.

Do not use Humulin N:

- if the insulin substance (the white material) remains visibly separated from the liquid after mixing or
- if there are clumps in the insulin after mixing, or
- if solid white particles stick to the walls of the cartridge, giving a frosted appearance.

If you see anything unusual in the appearance of the Humulin N suspension in your Pen or notice your insulin requirements changing, talk to your doctor.

Never attempt to remove the cartridge from the Humulin N Pen. Inspect the cartridge through the clear cartridge holder.

Storage

Not in-use (unopened): Humulin N Pens not in-use should be stored in a refrigerator, but not in the freezer.

In-use (opened): Humulin N Pens in-use should **NOT** be refrigerated but should be kept at room temperature [below 86°F (30°C)] away from direct heat and light. The Humulin N Pen you are currently using must be discarded **2 weeks** after the first use, even if it still contains Humulin N.

Do not use Humulin N after the expiration date stamped on the label or if it has been frozen.

INSTRUCTIONS FOR INSULIN PEN USE

It is important to read, understand, and follow the instructions in the Insulin Delivery Device User Manual before using. Failure to follow instructions may result in getting too much or too little insulin. The needle must be changed and the Pen must be primed to a stream of insulin (not just a few drops) before each injection to make sure the Pen is ready to dose. You may need to prime a new Pen up to six times before a stream of insulin appears. Performing these steps before each injection is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use.

Every time you inject:

- Use a new needle.
- Prime to a stream of insulin (not just a few drops) to make sure the Pen is ready to dose.
- Make sure you got your full dose.

NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES.

PREPARING FOR INJECTION

1. Wash your hands.
2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the previous injection site. The usual sites of injection are abdomen, thighs, and arms.
3. Follow the instructions in your Insulin Delivery Device User Manual to prepare for injection.
4. After injecting the dose, pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.**
5. After the injection, remove the needle from the Humulin N Pen. **Do not reuse needles.**
6. Place the used needle in a puncture-resistant disposable container and properly dispose of the puncture-resistant container 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 diabetes is different, this schedule has been individualized for you.

Your usual dose of Humulin N may be affected by changes in your diet, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your Humulin N 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 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

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, talk to your doctor.

Medication

Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin requirements may be reduced in the presence of drugs that lower blood glucose or affect how your body responds to insulin, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, certain antidepressants and some kidney and blood pressure medicines. Your Health Care Professional may be aware of other medications that may affect your diabetes control. Therefore, always discuss any medications you are taking with your doctor.

Exercise

Exercise may lower your body's need for insulin during and for some time after the physical activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise involves the area of injection site (for example, the leg should not be used for injection just prior to running). Discuss with your doctor how you should adjust your insulin regimen to accommodate exercise.

Travel

When traveling across more than 2 time zones, you should talk to your doctor concerning adjustments in your insulin schedule.

COMMON PROBLEMS OF DIABETES

Hypoglycemia (Low Blood Sugar)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. **Missing or delaying meals.**
2. Taking too much insulin.
3. Exercising or working more than usual.
4. An infection or illness associated with diarrhea or vomiting.
5. A change in the body's need for insulin.
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease.
7. Interactions with certain drugs, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, certain antidepressants and some kidney and blood pressure medicines.
8. Consumption of alcoholic beverages.

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

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

Signs of severe hypoglycemia can include:

- | | |
|-------------------|------------|
| • disorientation | • seizures |
| • unconsciousness | • 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 insulin 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 hard candy 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 talk to your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)

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

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

In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in DKA (a life-threatening emergency). 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, blood and 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 pain, 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 (seen as an apparent depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either of these conditions, talk to 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, talk to 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 to insulin, call your doctor immediately.

ADDITIONAL INFORMATION

Information about diabetes may be obtained from your diabetes educator.

Additional information about diabetes and Humulin can be obtained by calling The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

Patient Information revised Month dd, yyyy

Pens manufactured by

**Eli Lilly and Company, Indianapolis, IN 46285, USA or
Lilly France, F-67640 Fegersheim, France**

for Eli Lilly and Company, Indianapolis, IN 46285, USA

Copyright © 1998, yyyy, Eli Lilly and Company. All rights reserved.

PRINTED IN USA

**INFORMATION FOR THE PATIENT
3 ML PREFILLED INSULIN DELIVERY DEVICE**

**HUMULIN[®] 70/30 Pen
70% HUMAN INSULIN
ISOPHANE SUSPENSION
AND
30% HUMAN INSULIN INJECTION
(rDNA ORIGIN)
100 UNITS PER ML (U-100)**

WARNINGS

THIS LILLY HUMAN INSULIN PRODUCT DIFFERS FROM ANIMAL-SOURCE INSULINS BECAUSE IT IS STRUCTURALLY IDENTICAL TO THE INSULIN PRODUCED BY YOUR BODY'S PANCREAS AND BECAUSE OF ITS UNIQUE MANUFACTURING PROCESS.

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

SOME PATIENTS TAKING HUMULIN[®] (HUMAN INSULIN, rDNA ORIGIN) 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 USER MANUAL AND THIS "INFORMATION FOR THE PATIENT" INSERT BEFORE USING THIS PRODUCT.

THE PEN MUST BE PRIMED TO A STREAM OF INSULIN (NOT JUST A FEW DROPS) BEFORE EACH INJECTION TO MAKE SURE THE PEN IS READY TO DOSE. YOU MAY NEED TO PRIME A NEW PEN UP TO SIX TIMES BEFORE A STREAM OF INSULIN APPEARS.

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

DIABETES

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

To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near-normal level. You have been instructed to test your blood and/or your 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 or your hemoglobin A_{1c} (HbA_{1c}) is more than 7%, you should talk to your doctor. A change in your diabetes therapy may be needed. If your blood tests consistently show below-normal 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 by your doctor.

Always keep an extra supply of insulin 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.

70/30 HUMAN INSULIN

Description

Humulin is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce human insulin. Humulin 70/30 is a mixture of 70% Human Insulin Isophane Suspension and 30% Human Insulin Injection, (rDNA origin). It is an intermediate-acting insulin combined with the more rapid onset of action of Regular human insulin. The duration of activity may last up to 24 hours following injection. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of Humulin 70/30 is dependent on dose, site of injection, blood supply, temperature, and physical activity. Humulin 70/30 is a sterile suspension and is for subcutaneous injection only. It should not be used intravenously or intramuscularly. The concentration of Humulin 70/30 is 100 units/mL (U-100).

Identification

Human insulin from Eli Lilly and Company has the trademark Humulin.

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.

The Humulin 70/30 Pen is available in boxes of 5 prefilled insulin delivery devices ("insulin Pens"). The Humulin 70/30 Pen is not designed to allow any other insulin to be mixed in its cartridge, or for the cartridge to be removed.

Always check the carton and the Pen label for the name and letter designation of the insulin you receive from your pharmacy to make sure it is the same as prescribed by your doctor.

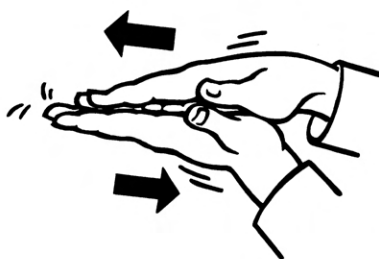


Figure 1.

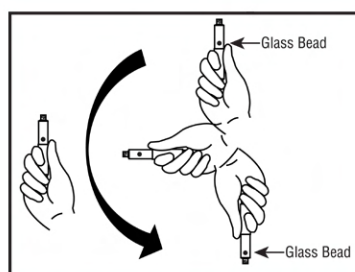


Figure 2.

Always check the appearance of Humulin 70/30 suspension in your insulin Pen before using. A cartridge of Humulin 70/30 contains a small glass bead to assist in mixing. Roll the Pen back and forth between the palms 10 times (see Figure 1). Gently turn the Pen up and down 10 times until the insulin is evenly mixed (see Figure 2). If not evenly mixed, repeat the above steps until contents are mixed. Pens containing Humulin 70/30 suspension should be examined frequently.

Do not use Humulin 70/30:

- if the insulin substance (the white material) remains visibly separated from the liquid after mixing or
- if there are clumps in the insulin after mixing, or
- if solid white particles stick to the walls of the cartridge, giving a frosted appearance.

If you see anything unusual in the appearance of the Humulin 70/30 suspension in your Pen or notice your insulin requirements changing, talk to your doctor.

Never attempt to remove the cartridge from the Humulin 70/30 Pen. Inspect the cartridge through the clear cartridge holder.

Storage

Not in-use (unopened): Humulin 70/30 Pens not in-use should be stored in a refrigerator, but not in the freezer.

In-use (opened): Humulin 70/30 Pens in-use should **NOT** be refrigerated but should be kept at room temperature [below 86°F (30°C)] away from direct heat and light. The Humulin 70/30 Pen you are currently using must be discarded **10 days** after the first use, even if it still contains Humulin 70/30.

Do not use Humulin 70/30 after the expiration date stamped on the label or if it has been frozen.

INSTRUCTIONS FOR INSULIN PEN USE

It is important to read, understand, and follow the instructions in the Insulin Delivery Device User Manual before using. Failure to follow instructions may result in getting too much or too little insulin. The needle must be changed and the Pen must be primed to a stream of insulin (not just a few drops) before each injection to make sure the Pen is ready to dose. You may need to prime a new Pen up to six times before a stream of insulin appears. Performing these steps before each injection is important to confirm that insulin comes out when you push the injection button, and to remove air that may collect in the insulin cartridge during normal use.

Every time you inject:

- Use a new needle.
- Prime to a stream of insulin (not just a few drops) to make sure the Pen is ready to dose.
- Make sure you got your full dose.

NEVER SHARE INSULIN PENS, CARTRIDGES, OR NEEDLES.

PREPARING FOR INJECTION

1. Wash your hands.
2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the previous injection site. The usual sites of injection are abdomen, thighs, and arms.
3. Follow the instructions in your Insulin Delivery Device User Manual to prepare for injection.
4. After injecting the dose, pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.**
5. After the injection, remove the needle from the Humulin 70/30 Pen. **Do not reuse needles.**
6. Place the used needle in a puncture-resistant disposable container and properly dispose of the puncture-resistant container 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 diabetes is different, this schedule has been individualized for you.

Your usual dose of Humulin 70/30 may be affected by changes in your diet, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your Humulin 70/30 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 frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

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, talk to your doctor.

Medication

Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin requirements may be reduced in the presence of drugs that lower blood glucose or affect how your body responds to insulin, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, certain antidepressants and some kidney and blood pressure medicines. Your Health Care Professional may be aware of other medications that may affect your diabetes control. Therefore, always discuss any medications you are taking with your doctor.

Exercise

Exercise may lower your body's need for insulin during and for some time after the physical activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise involves the area of injection site (for example, the leg should not be used for injection just prior to running). Discuss with your doctor how you should adjust your insulin regimen to accommodate exercise.

Travel

When traveling across more than 2 time zones, you should talk to your doctor concerning adjustments in your insulin schedule.

COMMON PROBLEMS OF DIABETES

Hypoglycemia (Low Blood Sugar)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. **Missing or delaying meals.**
2. Taking too much insulin.
3. Exercising or working more than usual.
4. An infection or illness associated with diarrhea or vomiting.
5. A change in the body's need for insulin.
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease.
7. Interactions with certain drugs, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, certain antidepressants and some kidney and blood pressure medicines.
8. Consumption of alcoholic beverages.

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

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

Signs of severe hypoglycemia can include:

- | | |
|-------------------|------------|
| • disorientation | • seizures |
| • unconsciousness | • 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 insulin 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 hard candy 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 talk to your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)

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

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

In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in DKA (a life-threatening emergency). 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, blood and 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 pain, 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 (seen as an apparent depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either of these conditions, talk to 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, talk to 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 to insulin, call your doctor immediately.

ADDITIONAL INFORMATION

Information about diabetes may be obtained from your diabetes educator.

Additional information about diabetes and Humulin can be obtained by calling The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

Patient Information revised Month dd, yyyy

Pens manufactured by

**Eli Lilly and Company, Indianapolis, IN 46285, USA or
Lilly France, F-67640 Fegersheim, France**

for Eli Lilly and Company, Indianapolis, IN 46285, USA

Copyright © 1998, yyyy, Eli Lilly and Company. All rights reserved.

PRINTED IN USA

HUMALOG[®]

INSULIN LISPRO INJECTION, USP

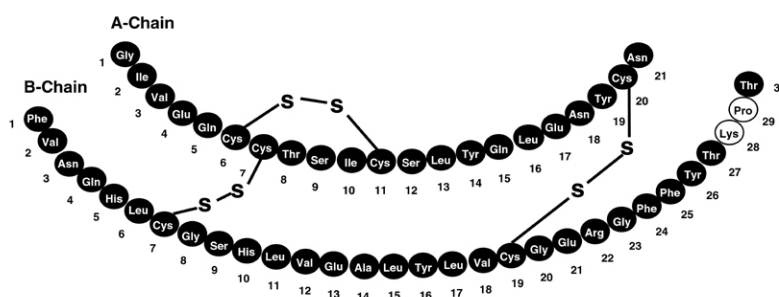
(rDNA ORIGIN)

100 UNITS PER ML (U-100)

DESCRIPTION

Humalog[®] [insulin lispro injection, USP (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 to produce insulin lispro.

Humalog has the following primary structure:



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.

The vials, cartridges, and Pens 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 Metacresol, 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 to 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 Regular human insulin, but its effect is more rapid and of shorter duration. The glucose-lowering activity of Humalog and Regular human insulin is comparable when administered to nondiabetic subjects by the intravenous route.

Pharmacokinetics

Absorption and Bioavailability — Humalog is as bioavailable as Regular human insulin, with absolute bioavailability ranging between 55% to 77% with doses between 0.1 to 0.2 U/kg,

inclusive. Studies in nondiabetic subjects and patients with type 1 (insulin-dependent) diabetes demonstrated that Humalog is absorbed faster than Regular human insulin (U-100) (*see* Figure 1). In nondiabetic subjects given subcutaneous doses of Humalog ranging from 0.1 to 0.4 U/kg, peak serum concentrations were observed 30 to 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type 1 diabetes. The pharmacokinetic profiles of Humalog and Regular human insulin are comparable to one another when administered to nondiabetic subjects by the intravenous route. Humalog was absorbed at a consistently faster rate than Regular human insulin in healthy male volunteers given 0.2 U/kg Regular human insulin or Humalog at abdominal, deltoid, or femoral subcutaneous 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). Humalog has less intra- and inter-patient variability compared with Regular human insulin.

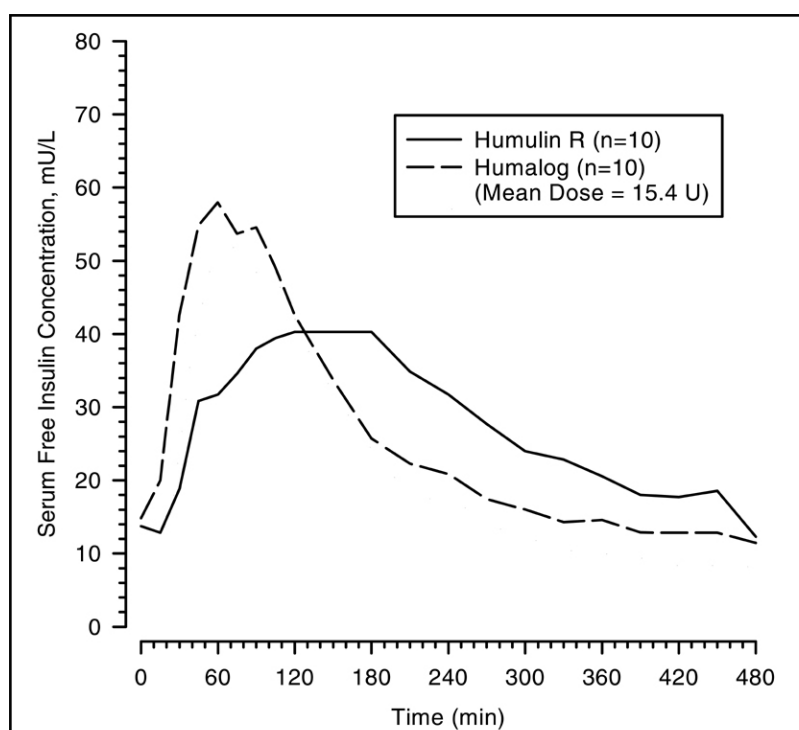


Figure 1: Serum Humalog and Insulin Levels After Subcutaneous Injection of Regular Human Insulin or Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes. *

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

Distribution — The volume of distribution following injection of Humalog is identical to that of Regular human insulin, with a range of 0.26 to 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 Regular human insulin.

Elimination — When Humalog is given subcutaneously, its $t_{1/2}$ is shorter than that of Regular human insulin (1 versus 1.5 hours, respectively). When given intravenously, Humalog and Regular human 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 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 (*see* Figure 2). 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 presented in Figure 2 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).

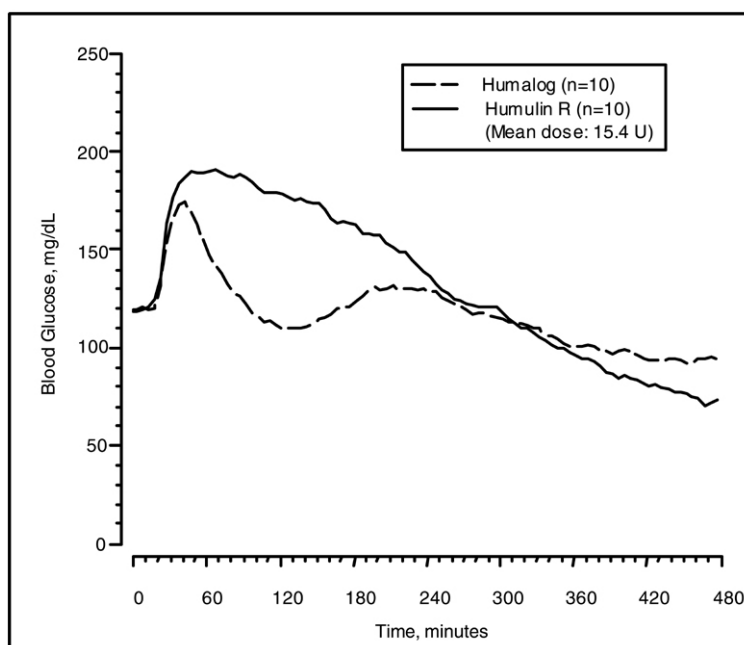


Figure 2: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes. *

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

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, sub-group analysis based on age and gender did not indicate any difference in postprandial glucose parameters between Humalog and Regular human insulin.

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

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

Obesity — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics 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 observed 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. In a study of 25 patients with type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between Humalog and Regular human

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, 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. 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 with patients with no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption and elimination when compared with Regular human insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog, may be necessary in patients with hepatic dysfunction.

CLINICAL STUDIES

In open-label, cross-over studies of 1008 patients with type 1 diabetes and 722 patients with type 2 (non-insulin-dependent) diabetes, Humalog reduced postprandial glucose compared with Regular human insulin (*see* Table 1). The clinical significance of improvement in postprandial hyperglycemia has not been established.

Table 1: 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 1, N=1008		
Glycemic Parameter, (mg/dL)	Humalog ^a	Humulin R ^{a*}
Fasting Blood Glucose	209.5 ± 91.6	204.1 ± 89.3
1-Hour Postprandial	232.4 ± 97.7	250.0 ± 96.7
2-Hour Postprandial	200.9 ± 95.4	231.7 ± 103.9
HbA _{1c} (%)	8.2 ± 1.5	8.2 ± 1.5
Type 2, N=722		
Glycemic Parameter, (mg/dL)	Humalog ^a	Humulin R ^a
Fasting Blood Glucose	192.1 ± 67.9	183.1 ± 66.1
1-Hour Postprandial	238.1 ± 79.7	250.0 ± 75.2
2-Hour Postprandial	217.4 ± 83.2	236.5 ± 80.6
HbA _{1c} (%)	8.2 ± 1.3	8.2 ± 1.4

^a Mean ± Standard Deviation.

* REGULAR insulin human injection, USP (rDNA origin).

In 12-month parallel studies in patients with type 1 and type 2 diabetes, HbA_{1c} did not differ between patients treated with Regular human insulin and those treated with Humalog.

Hypoglycemia — While the overall rate of hypoglycemia did not differ between patients with type 1 and type 2 diabetes treated with Humalog compared with Regular human insulin, patients with type 1 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.

Humalog in Combination with Sulfonylurea Agents — In a two-month study in patients with fasting hyperglycemia despite maximal dosing with sulfonylureas (SU), patients were randomized to one of three treatment regimens; Humulin[®] NPH at bedtime plus SU, Humalog three times a day before meals plus SU, or Humalog three times a day before meals and Humulin NPH at bedtime. The combination of Humalog and SU resulted in an improvement in HbA_{1c} accompanied by a weight gain (*see* Table 2).

Table 2: Results of a Two-Month Study in Which Humalog Was Added to Sulfonylurea Therapy in Patients Not Adequately Controlled on Sulfonylurea Alone

	Humulin N h.s. + SU ^a	Humalog a.c. + SU	Humalog a.c. + Humulin N h.s.
Randomized (n)	135	139	149
HbA _{1c} (%) at baseline	9.9	10.0	10.0
HbA _{1c} (%) at 2-months	8.7	8.4	8.5
HbA _{1c} (%) change from baseline	-1.2	-1.6	-1.4
Weight gain at 2-months (kg)	0.6	1.2	1.5
Hypoglycemia* (events/mo)	0.11	0.03	0.09
Number of injections	1	3	4
Total insulin dose (U/kg) at 2-months	0.23	0.33	0.52

^a a.c.-three times a day before meals. h.s.-at bedtime. SU-oral sulfonylurea agent.

* blood glucose \leq 36 mg/dL or needing assistance from third party.

Humalog in External Insulin Pumps — To evaluate the administration of Humalog via external insulin pumps, two open-label cross-over design studies were performed in patients with type 1 diabetes. One study involved 39 patients treated for 24 weeks with Humalog or Regular human insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.8% to 7.2% in the Humalog-treated patients and from 7.8% to 7.5% in the Regular human insulin-treated patients. Another study involved 60 patients treated for 24 weeks with either Humalog or Regular human insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.7% to 7.4% in the Humalog-treated patients and remained unchanged from 7.7% in the Regular human insulin-treated patients. Rates of hypoglycemia were comparable between treatment groups in both studies. Humalog administration in insulin pumps has not been studied in patients with type 2 diabetes.

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 Regular human insulin. Therefore, in patients with type 1 diabetes, Humalog should be used in regimens that include a longer-acting insulin. However, in patients with type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Humalog may be used in an external insulin pump, but should not be diluted or mixed with any other insulin when used in the pump.

CONTRAINDICATIONS

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

WARNINGS

This human insulin analog differs from Regular human insulin by its rapid onset of action as well as a shorter duration of activity. When used as a meal-time insulin, the dose of Humalog should be given within 15 minutes before or immediately after the meal. Because of the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an external insulin pump). Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using an external insulin pump.

Hypoglycemia is the most common adverse effect associated with 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.

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, or method of manufacture may result in the need for a change in dosage.

External Insulin Pumps: When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin. Patients should carefully read and follow the external insulin pump manufacturer's instructions and the Patient Information leaflet before using Humalog.

Physicians should carefully evaluate information on external insulin pump use in this Humalog physician package insert and in the external insulin pump manufacturer's instructions. If unexplained hyperglycemia or ketosis occurs during external insulin pump use, prompt identification and correction of the cause is necessary. The patient may require interim therapy with subcutaneous insulin injections (*see PRECAUTIONS, For Patients Using External Insulin Pumps, and DOSAGE AND ADMINISTRATION*).

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 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 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 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 — The requirements for insulin 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, 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. 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=0.053). 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.

Usage in External Insulin Pumps — **The infusion set (reservoir syringe, tubing, and catheter), Disetronic® D-TRON®^{2,3} or D-TRON®^{2,3}plus cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced and a new infusion site selected every 48 hours or less. Humalog in the external insulin pump should not be exposed to temperatures above 37°C (98.6°F).**

In the D-TRON®^{2,3} or D-TRON®^{2,3}plus pump, Humalog 3 mL cartridges may be used for up to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion site should be selected every 48 hours or less.

When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin (*see* INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, *For Patients Using External Insulin Pumps, Mixing of Insulins*, DOSAGE AND ADMINISTRATION, and *Storage*).

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 hemoglobin A_{1c} 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 Patient Information leaflet for timing of Humalog dosing (≤15 minutes before or immediately after a meal), storing insulin, and common adverse effects.

For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read the Patient Information leaflet that accompanies the drug product and the User Manual that accompanies the delivery device and re-read them each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen to a stream of insulin, and properly dispose of needles. Patients should be advised not to share their Pens with others.

For Patients Using External Insulin Pumps: Patients using an external infusion pump should be trained in intensive insulin therapy and in the function of their external insulin pump and pump accessories. Humalog was tested in the MiniMed®¹ Models 506, 507, and 508 insulin pumps using MiniMed®¹ Polyfin®¹ infusion sets. Humalog was also tested in Disetronic®² H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), and the Disetronic D-TRON®^{2,3} and D-TRON®^{2,3}plus insulin pumps (with Humalog 3 mL cartridges) using Disetronic Rapid®² infusion sets.

The infusion set (reservoir syringe, tubing, catheter), D-TRON®^{2,3} or D-TRON®^{2,3}plus cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced, and a new infusion site selected every 48 hours or less. Humalog in the external pump should not be exposed to temperatures above 37°C (98.6°F). A Humalog 3 mL cartridge used in the D-TRON®^{2,3} or D-TRON®^{2,3}plus pump should be discarded after 7 days, even if it still

contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected.

Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

Laboratory Tests

As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} 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 (*see* CLINICAL PHARMACOLOGY).

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

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.” Mixing Humalog with Humulin N or Humulin® U does not decrease the absorption rate or the total bioavailability of Humalog. Given alone or mixed with Humulin N, Humalog results in a more rapid absorption and glucose-lowering effect compared with Regular human insulin.

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, such as Humulin N or Humulin U, 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.

The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the cartridge, for the Humalog in the cartridge to be diluted or for the cartridge to be refilled with insulin. Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog, Humalog Mix75/25, or Humalog Mix50/50. 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 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 with Humalog, Humalog Mix75/25, or Humalog Mix50/50 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 limited 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

In a 9-month, cross-over study of pre-pubescent children (n=60), aged 3 to 11 years, comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group: Regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%, and Humalog immediately after meals 8.5%. In an 8-month, cross-over study of adolescents (n=463), aged 9 to 19 years, comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group: Regular human insulin 30 to 45 minutes before meals 8.7% and Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all three treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the Humalog vial, the shelf-life may be reduced (*see* DOSAGE AND ADMINISTRATION).

Geriatric Use

Of the total number of subjects (n=2834) in eight clinical studies of Humalog, twelve percent (n=338) were 65 years of age or over. The majority of these were patients with type 2 diabetes. HbA_{1c} values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of Humalog action have not been performed.

ADVERSE REACTIONS

Clinical studies comparing Humalog with Regular human 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, including use in select external insulin pumps (*see* DOSAGE AND ADMINISTRATION, *External Insulin Pumps*). Dosage regimens of Humalog will vary among patients and should be determined by the healthcare provider familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to Regular human insulin (i.e., one unit of Humalog has the same glucose-lowering effect as one unit of Regular human 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 or immediately after a meal. Regular human insulin is best given 30 to 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 are known to be affected by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently faster rate than Regular human insulin in healthy male volunteers given 0.2 U/kg Regular human 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 Regular human 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.

Humalog in a vial may be diluted with STERILE DILUENT for Humalog[®], Humulin[®] N, Humulin[®] R, Humulin[®] 70/30, and Humulin[®] R U-500 to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog contained in a cartridge or Humalog used in an external insulin pump.

Parenteral drug products should be inspected visually before use 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.

The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge to be refilled with insulin.

External Insulin Pumps — Humalog was tested in MiniMed[®] 1 Models 506, 507, and 508 insulin pumps using MiniMed[®] 1 Polyfin[®] 1 infusion sets. Humalog was also tested in the Disetronic[®] 2 H-TRONplus[®] V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the Disetronic D-TRON[®] 2,3 and D-TRON[®] 2,3 plus pumps (with Humalog 3 mL cartridges) using Disetronic Rapid[®] 2 infusion sets.

Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

HOW SUPPLIED

Humalog [insulin lispro injection, USP (rDNA origin)] is available in the following package sizes: each presentation containing 100 units insulin lispro per mL (U-100).

10 mL vials	NDC 0002-7510-01 (VL-7510)
5 x 3 mL cartridges ³	NDC 0002-7516-59 (VL-7516)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8725-59 (HP-8725)
5 x 3 mL prefilled insulin delivery devices (KwikPen™)	NDC 0002-8799-59 (HP-8799)

1 MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

2 Disetronic®, H-TRONplus®, D-TRON®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.

3 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3 mL insulin delivery device and Disetronic D-

TRON® and D-TRON®plus pumps. Autopen® is a registered trademark of Owen Mumford, Ltd. HumaPen®,

HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD are trademarks of Eli Lilly and Company.

Other product and company names may be the trademarks of their respective owners.

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

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Cartridge	28 days	Until expiration date	28 days, Do not refrigerate.
3 mL Pen and KwikPen (prefilled)	28 days	Until expiration date	28 days, Do not refrigerate.

Use in an External Insulin Pump — A Humalog 3 mL cartridge used in the D-TRON®^{2,3} or D-TRON®^{2,3}plus should be discarded after 7 days, even if it still contains Humalog. Infusion sets, D-TRON®^{2,3} and D-TRON®^{2,3}plus cartridge adapters, and Humalog in the external insulin pump reservoir should be discarded every 48 hours or less.

Literature revised Month dd, yyyy

KwikPens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA
Pens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA or
Lilly France, F-67640 Fegersheim, France
Vials manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA or
Hospira, Inc., Lake Forest, IL 60045, USA or
Lilly France, F-67640 Fegersheim, France
Cartridges manufactured by
Lilly France, F-67640 Fegersheim, France
for Eli Lilly and Company, Indianapolis, IN 46285, USA

www.humalog.com

Copyright © 2007, yyyy Eli Lilly and Company. All rights reserved.

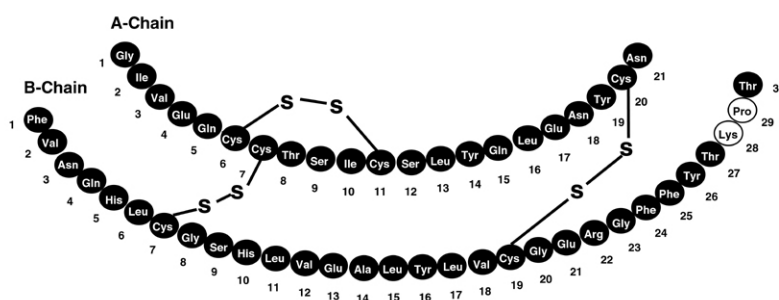
PRINTED IN USA

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 to produce 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:



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 Pens 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 Metacresol, 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 to 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 with 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 to 0.4 U/kg, peak serum concentrations were observed 30 to 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type 1 diabetes.

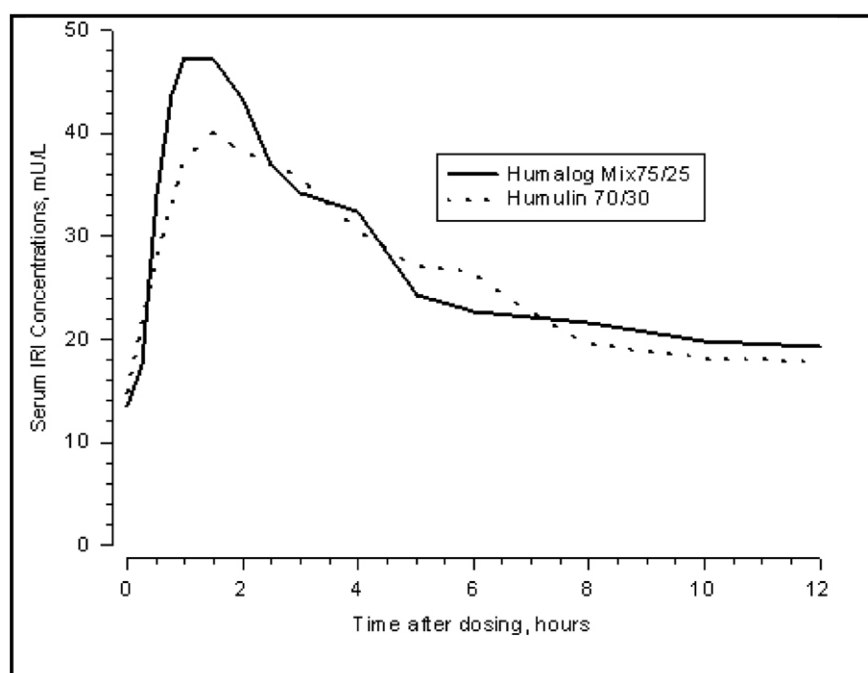


Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous Injection of Humalog Mix75/25 or Humulin 70/30 in Healthy Nondiabetic Subjects.

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 healthy 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 (*see* Figure 1). Identical results were found in patients with type 1 diabetes. The rapid absorption characteristics of Humalog are maintained with Humalog Mix75/25 (*see* Figure 1).

Figure 1 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 to 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 and 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 General under PRECAUTIONS*).

In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and glucose-lowering activity of Humalog, Humalog[®] Mix50/50[™], Humalog Mix75/25, and insulin lispro protamine suspension (NPL component) were compared (*see Figure 2*). 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, pharmacodynamics of Humalog Mix75/25 and Humulin 70/30 were assessed and are presented in Figure 3. Humalog Mix75/25 has a duration of activity similar to that of Humulin 70/30.

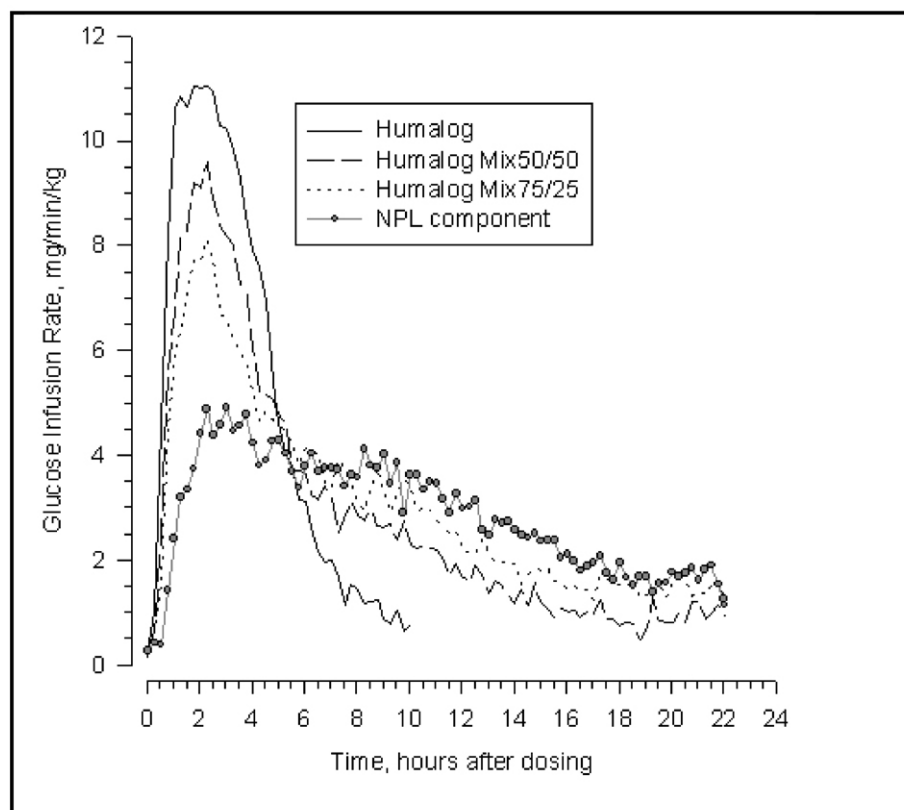


Figure 2: Insulin Activity After Injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic Subjects.

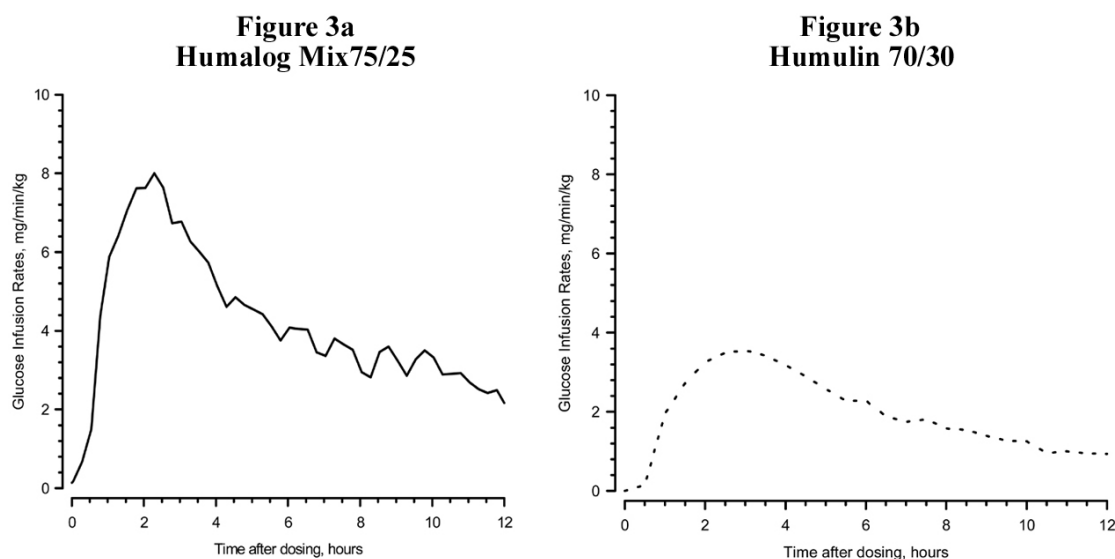


Figure 3: Insulin Activity After Injection of Humalog Mix75/25 and Humulin 70/30 in Nondiabetic Subjects.

Figures 2 and 3 represent insulin activity profiles as measured by glucose clamp studies in healthy nondiabetic subjects.

Figure 2 shows the time activity profiles of Humalog, Humalog Mix50/50, Humalog Mix75/25, and insulin lispro protamine suspension (NPL component).

Figure 3 is a comparison of the time activity profiles of Humalog Mix75/25 (see Figure 3a) and of Humulin 70/30 (see Figure 3b) 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, sub-group analysis based on 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 pharmacodynamics of Humalog Mix75/25 has not been studied.

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

Obesity — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics 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/m², 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 pharmacodynamics 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 Regular human 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 pharmacodynamics 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 with patients with no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption and elimination when compared with 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 injection, (rDNA origin), 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 with 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, or method of manufacture 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 Humalog Mix75/25 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 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 hemoglobin A_{1c} 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 Patient Information leaflet for information on normal appearance, timing of dosing (within 15 minutes before a meal), storing, and common adverse effects.

For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read the Patient Information leaflet that accompanies the drug product and the User Manual that accompanies the delivery device and re-read them each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen to a stream of insulin, 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 hemoglobin A_{1c} 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 that increase insulin sensitivity or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog, Humalog Mix75/25, or Humalog Mix50/50. 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, Humalog Mix75/25, or Humalog Mix50/50 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 Pharmacodynamic 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 healthcare provider 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 with 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 to 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 [75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)] is available in the following package sizes: each presentation containing 100 units insulin lispro per mL (U-100).

10 mL vials	NDC 0002-7511-01 (VL-7511)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8794-59 (HP-8794)
5 x 3 mL prefilled insulin delivery devices (KwikPen™)	NDC 0002-8797-59 (HP-8797)

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

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen and KwikPen (prefilled)	10 days	Until expiration date	10 days. Do not refrigerate.

Literature revised Month dd, yyyy

KwikPens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA
Pens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA or
Lilly France, F-67640 Fegersheim, France
Vials manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA or
Lilly France, F-67640 Fegersheim, France
for Eli Lilly and Company, Indianapolis, IN 46285, USA

www.humalog.com

Copyright © 2007, yyyy, Eli Lilly and Company. All rights reserved.

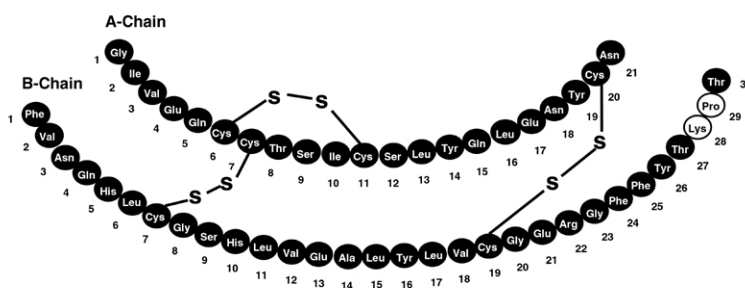
PRINTED IN USA

HUMALOG[®] Mix50/50[™]
50% INSULIN LISPRO PROTAMINE SUSPENSION AND
50% INSULIN LISPRO INJECTION
(rDNA ORIGIN)
100 UNITS PER ML (U-100)

DESCRIPTION

Humalog[®] Mix50/50[™] [50% insulin lispro protamine suspension and 50% 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 to produce 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:



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 Mix50/50 vials and Pens contain a sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

Each milliliter of Humalog Mix50/50 injection contains insulin lispro 100 units, 0.19 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 2.20 mg Metacresol, zinc oxide content adjusted to provide 0.0305 mg zinc ion, 0.89 mg phenol, and Water for Injection. Humalog Mix50/50 has a pH of 7.0 to 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 Mix50/50, 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 Mix50/50, 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.

Pharmacokinetics

Absorption — Studies in nondiabetic subjects and patients with type 1 (insulin-dependent) diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix50/50, is absorbed faster than Regular human insulin (U-100). In nondiabetic subjects given subcutaneous doses of Humalog ranging from 0.1 to 0.4 U/kg, peak serum concentrations were observed 30 to 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type 1 diabetes.

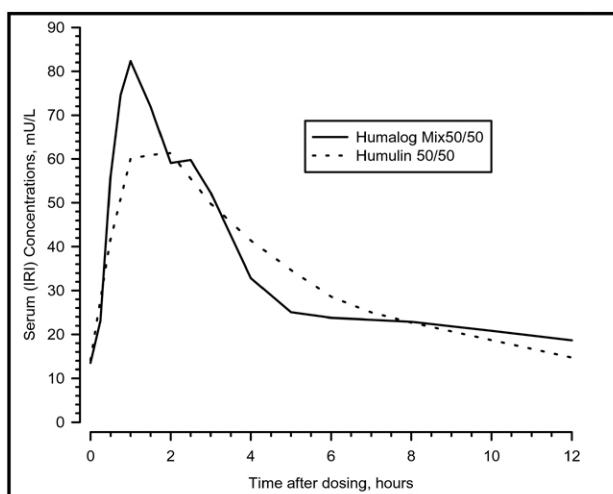


Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous Injection of Humalog Mix50/50 or Humulin 50/50 in Healthy Nondiabetic Subjects.

Humalog Mix50/50 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 healthy nondiabetic subjects given subcutaneous doses (0.3 U/kg) of Humalog Mix50/50, peak serum concentrations were observed 45 minutes to 13.5 hours (median, 60 minutes) after dosing (*see* Figure 1). In patients with type 1 diabetes, peak serum concentrations were observed 45 minutes to 120 minutes (median, 60 minutes) after dosing. The rapid absorption characteristics of Humalog are maintained with Humalog Mix50/50 (*see* Figure 1).

Direct comparison of Humalog Mix50/50 and Humulin 50/50 was not performed. However, a cross-study comparison shown in Figure 1 suggests that Humalog Mix50/50 has a more rapid absorption than Humulin 50/50.

Distribution — Radiolabeled distribution studies of Humalog Mix50/50 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 to 0.36 L/kg.

Metabolism — Human metabolism studies of Humalog Mix50/50 have not been conducted. Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of Humalog Mix50/50, is identical to that of Regular human insulin.

Elimination — Humalog Mix50/50 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 Mix50/50 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 Mix50/50 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 Mix50/50), may vary considerably in different individuals or within the same individual. The parameters of Humalog Mix50/50 activity (time of onset, peak time, and duration) as presented in Figures 2 and 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 General under PRECAUTIONS*).

In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and glucose-lowering activity of Humalog, Humalog Mix50/50, Humalog[®] Mix75/25[™], and insulin lispro protamine suspension (NPL component) were compared (*see Figure 2*). 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 Mix50/50.

Direct comparison between Humalog Mix50/50 and Humulin 50/50 was not performed. However, a cross-study comparison shown on Figure 3 suggests that Humalog Mix50/50 has a duration of activity that is similar to Humulin 50/50.

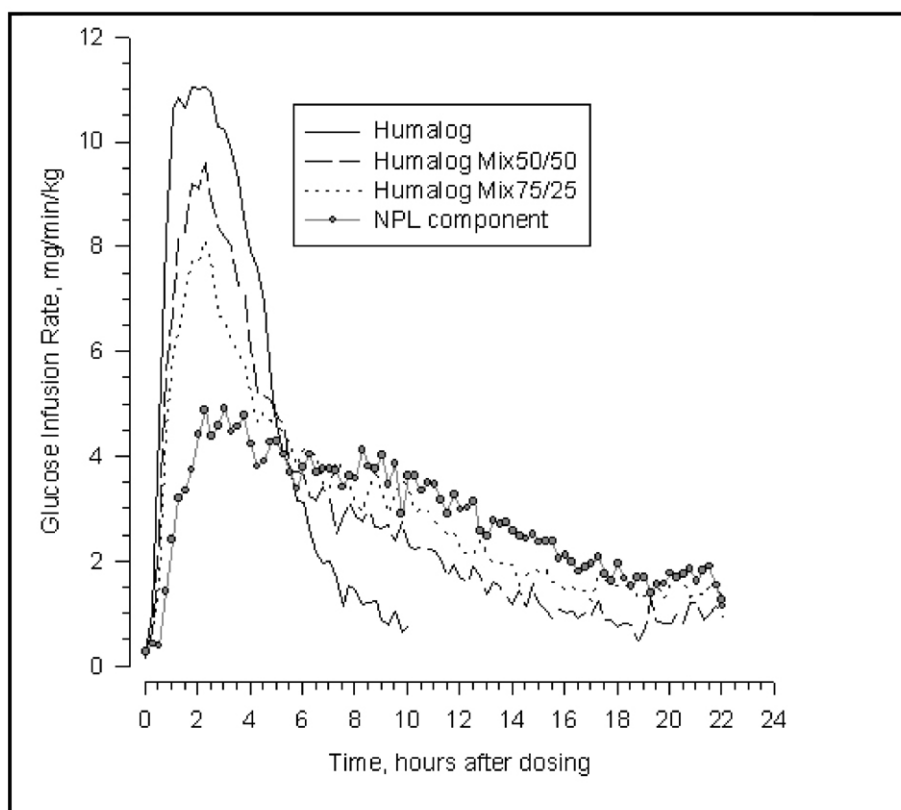


Figure 2: Glucose Infusion Rates (A Measure of Insulin Activity) After Injection of Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic Subjects.

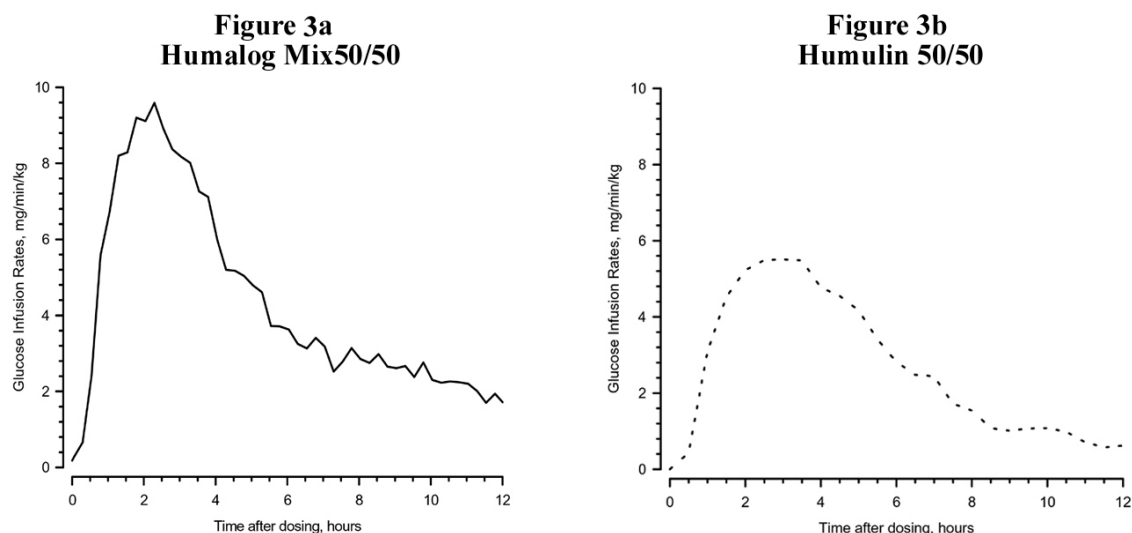


Figure 3: Insulin Activity After Subcutaneous Injection of Humalog Mix50/50 and Humulin 50/50 in Nondiabetic Subjects.

Figures 2 and 3 represent insulin activity profiles as measured by glucose clamp studies in healthy nondiabetic subjects.

Figure 2 shows the time activity profiles of Humalog, Humalog Mix75/25, Humalog Mix50/50, and insulin lispro protamine suspension (NPL component).

Figure 3 is a comparison of the time activity profiles of Humalog Mix50/50 (*see* Figure 3a) and of Humulin 50/50 (*see* Figure 3b) from two different studies.

Special Populations

Age and Gender — Information on the effect of age on the pharmacokinetics of Humalog Mix50/50 is unavailable. Pharmacokinetic and pharmacodynamic comparisons between men and women administered Humalog Mix50/50 showed no gender differences. In large Humalog clinical trials, sub-group analysis based on 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 pharmacodynamics of Humalog Mix50/50 has not been studied.

Pregnancy — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of Humalog Mix50/50 has not been studied.

Obesity — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of Humalog Mix50/50 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 observed between Humalog and Humulin[®] R with respect to postprandial glucose parameters.

Renal Impairment — The effect of renal impairment on the pharmacokinetics and pharmacodynamics of Humalog Mix50/50 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 Regular human 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 Mix50/50, 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 pharmacodynamics of Humalog Mix50/50 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 with patients with no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption and elimination when compared with Regular human insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog Mix50/50, may be necessary in patients with hepatic dysfunction.

INDICATIONS AND USAGE

Humalog Mix50/50, a mixture of 50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Based on cross-study comparisons of the pharmacodynamics of Humalog Mix50/50 and Humulin 50/50, it is likely that Humalog Mix50/50 has a more rapid onset of glucose-lowering activity compared with Humulin 50/50 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 Mix50/50 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 Mix50/50 should be given within 15 minutes before a meal.

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog Mix50/50. 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, or method of manufacture 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 Mix50/50 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 Humalog Mix50/50 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 Mix50/50. 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 Mix50/50 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 Mix50/50, 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 Mix50/50 and alternative therapies. Patients should not mix Humalog Mix50/50 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 hemoglobin A_{1c} 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 Patient Information leaflet for information on normal appearance, timing of dosing (within 15 minutes before a meal), storing, and common adverse effects.

For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read the Patient Information leaflet that accompanies the drug product and the User Manual that accompanies the delivery device and re-read them each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen to a stream of insulin, 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 Mix50/50 should be monitored by periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} 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 that increase insulin sensitivity or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics,

certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog, Humalog Mix75/25, or Humalog Mix50/50. 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, Humalog Mix75/25, or Humalog Mix50/50 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 Mix50/50 is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog Mix50/50 dose, meal plan, or both.

Pediatric Use

Safety and effectiveness of Humalog Mix50/50 in patients less than 18 years of age have not been established.

Geriatric Use

Clinical studies of Humalog Mix50/50 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 Mix50/50 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 Pharmacodynamic 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 Mix50/50 is intended only for subcutaneous administration. Humalog Mix50/50 should not be administered intravenously. Dosage regimens of Humalog Mix50/50 will vary among patients and should be determined by the healthcare provider 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. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

Direct comparison between Humalog Mix50/50 and Humulin 50/50 was not performed. However, a cross-study comparison shown in Figure 3 suggests that Humalog Mix50/50 has a duration of activity that is similar to Humulin 50/50.

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 Mix50/50 may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog Mix50/50 should be inspected visually before use. Humalog Mix50/50 should be used only if it appears uniformly cloudy after mixing. Humalog Mix50/50 should not be used after its expiration date.

HOW SUPPLIED

Humalog Mix50/50 [50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)] is available in the following package sizes: each presentation containing 100 units insulin lispro per mL (U-100).

10 mL vials	NDC 0002-7512-01 (VL-7512)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8793-59 (HP-8793)
5 x 3 mL prefilled insulin delivery devices (KwikPen™)	NDC 0002-8798-59 (HP-8798)

Storage — Humalog Mix50/50 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but not in the freezer. Do not use Humalog Mix50/50 if it has been frozen. Unrefrigerated [below 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain Humalog Mix50/50. Unrefrigerated [below 30°C (86°F)] Pens, and KwikPens must be used within 10 days or be discarded, even if they still contain Humalog Mix50/50. Protect from direct heat and light. See table below:

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen and KwikPen (prefilled)	10 days	Until expiration date	10 days. Do not refrigerate.

Literature revised Month dd, yyyy

KwikPens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA
Pens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA
Vials manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA or
Lilly France, F-67640 Fegersheim, France
for Eli Lilly and Company, Indianapolis, IN 46285, USA

www.humalog.com

Copyright © 2007, yyyy Eli Lilly and Company. All rights reserved.

PRINTED IN USA

Lilly

Prefilled Insulin Delivery Device
User Manual

Instructions for Use

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

Every time you inject:

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



Also, read the “Patient Information” enclosed in your Pen box.

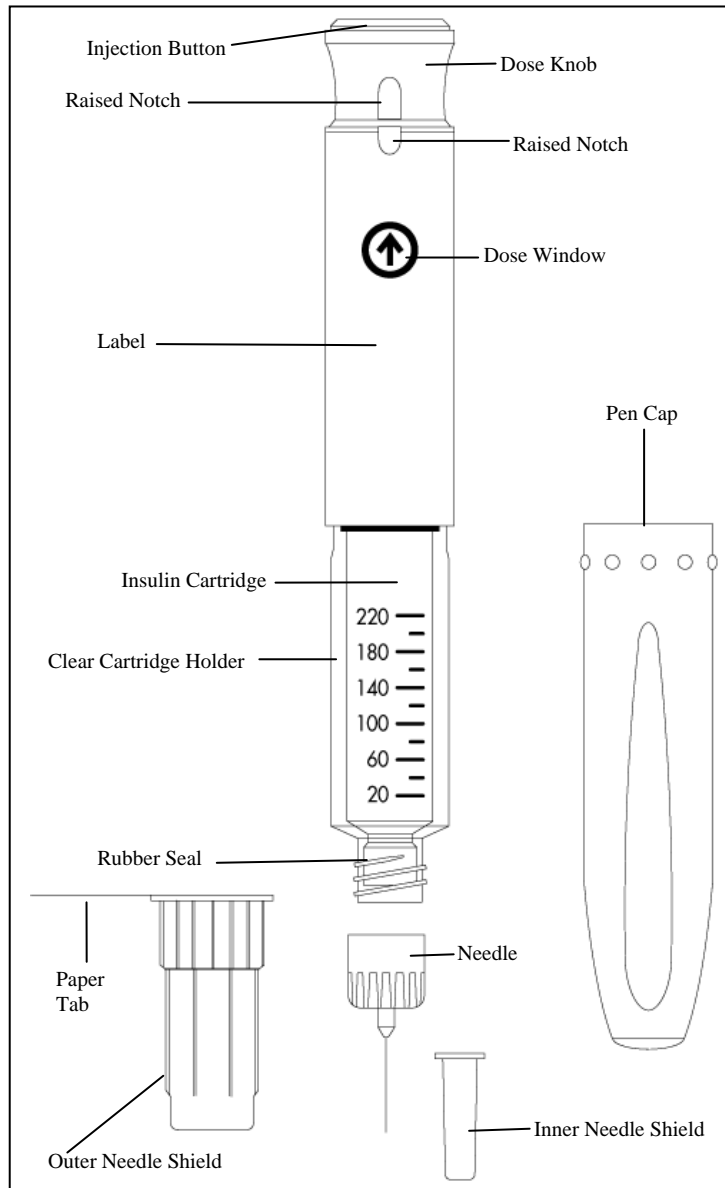
Pen Features

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

Table of Contents

Pen Parts	3
Important Notes.....	4
Preparing the Pen	6
Attaching the Needle	8
Priming the Pen.....	10
Setting a Dose.....	14
Injecting a Dose	16
Following an Injection.....	18
Questions and Answers	20

Pen Parts



Important Notes

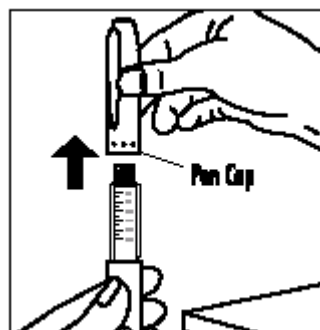
- **Read and follow all of these instructions carefully. If you do not follow these instructions completely, you may get too much or too little insulin.**
- **Use a new needle for each injection.**
 - **Be sure a needle is completely attached to the Pen before priming, setting the dose and injecting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

Important Notes (Continued)

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

I. Preparing the Pen

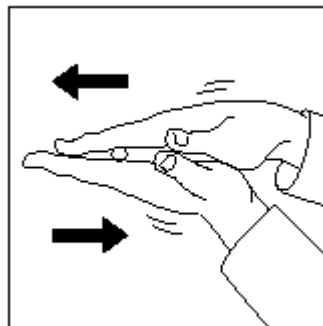
1. Before proceeding, refer to the “Patient Information” for instructions on checking the appearance of your insulin.
2. Check the label on the Pen to be sure the Pen contains the type of insulin that has been prescribed for you.
3. Always wash your hands before preparing your Pen for use.
4. Pull the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



I. Preparing the Pen (Continued)

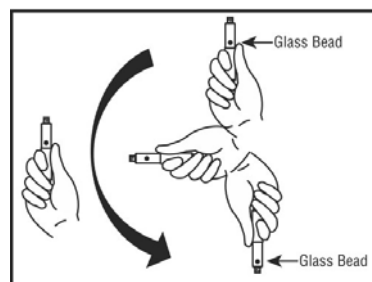
5. If your insulin is a suspension (cloudy):

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

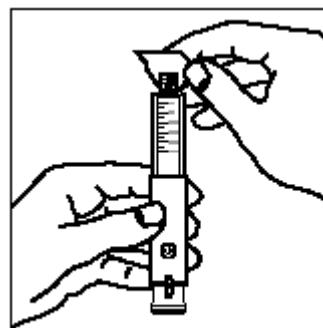


- b. Gently turn the Pen up and down 10 times until the insulin is evenly mixed.

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



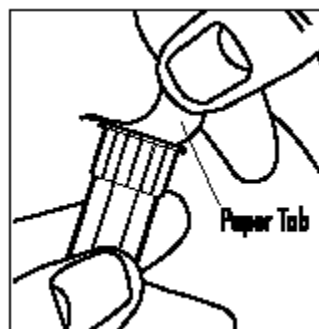
6. Use an alcohol swab to wipe the rubber seal on the end of the Pen.



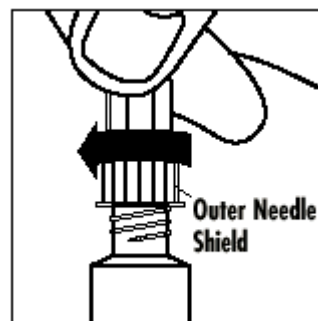
II. Attaching the Needle

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

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

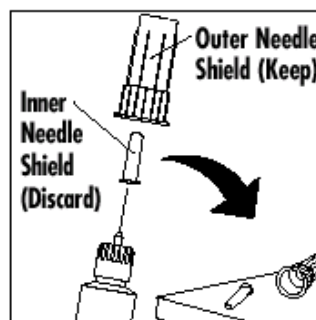


3. Attach the capped needle onto the end of the Pen by turning it clockwise until tight.



II. Attaching the Needle (Continued)

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

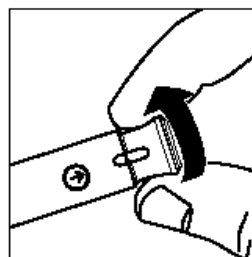


5. Remove the inner needle shield and discard.

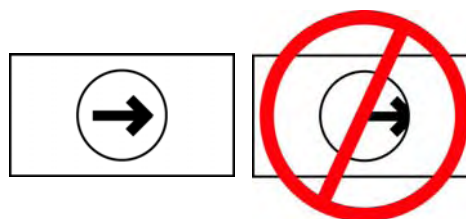
III. Priming the Pen

- **Prime every time.** The Pen must be primed to a stream of insulin (not just a few drops) before each injection to make sure the Pen is ready to dose.
- You may need to prime a new Pen up to six times before a stream of insulin appears.
- **If you do not prime, you may get too much or too little insulin.**
- **Always use a new needle for each injection.**

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



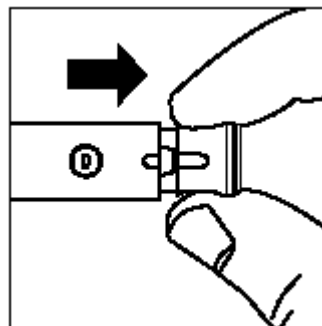
2. If you do not see the arrow in the center of the dose window, push in the injection button fully and turn the dose knob until the arrow is seen in the center of the dose window.



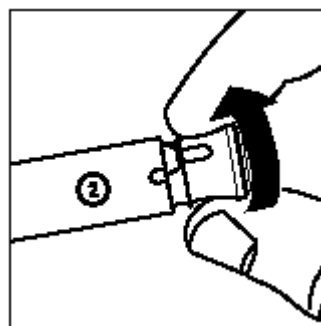
Correct

III. Priming the Pen (Continued)

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



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

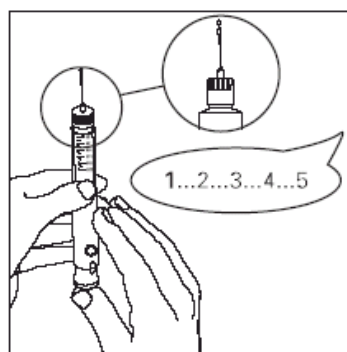


III. Priming the Pen (Continued)

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

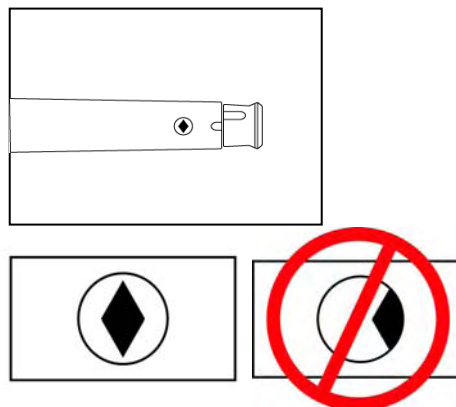
Using your thumb, if possible, push in the injection button completely. Keep pressing and continue to hold the injection button **firmly** while counting **slowly** to 5. You should see a stream of insulin come out of the tip of the needle.

If a stream of insulin does not come out of the tip of the needle, repeat steps 1 through 5. If after six attempts a stream of insulin does not come out of the tip of the needle, change the needle. Repeat steps 1 through 5 up to two more times. If you are still unable to get insulin flowing out of the needle, **do NOT use** the Pen. Contact your Health Care Professional or Lilly.



III. Priming the Pen (Continued)

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



Correct

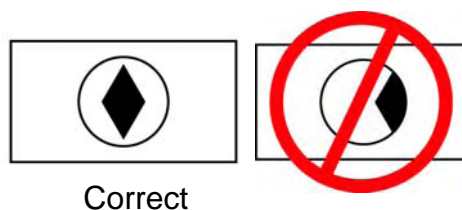
Note: A small air bubble may remain in the cartridge after the completion of the priming step. If you have properly primed the Pen, this small air bubble will not affect your insulin dose.

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

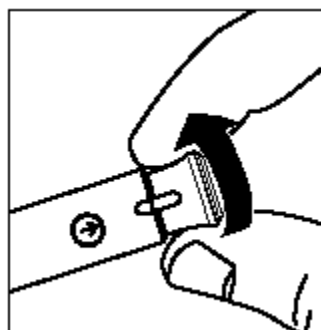
IV. Setting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**
 - **Caution: Do not push in the injection button while setting your dose. Failure to follow these instructions carefully may result in getting too much or too little insulin. If you accidentally push the injection button while setting your dose, you must prime the Pen again before injecting your dose. See Section III. “Priming the Pen”, pages 10-13.**
1. A diamond must be seen in the center of the dose window before setting your dose.

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

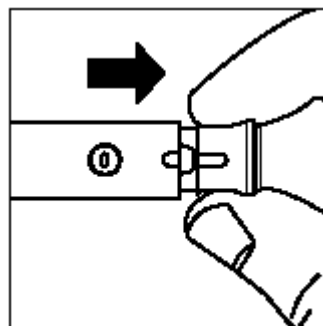


2. Turn the dose knob clockwise until the arrow (➡) is seen in the center of the dose window and the notches on the Pen and dose knob are in line.

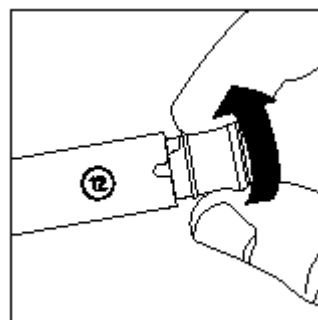


IV. Setting a Dose (Continued)

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



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



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

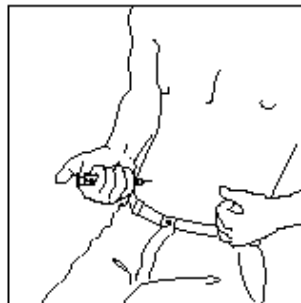
V. Injecting a Dose

- **Always use a new needle for each injection. Storing the Pen with the needle attached may allow insulin to leak from the Pen and air bubbles to form in the cartridge.**
- **Caution: Do not attempt to change the dose after you begin to push in the injection button. Failure to follow these instructions carefully may result in getting too much or too little insulin.**
- **The effort needed to push in the injection button may increase while you are injecting your insulin dose. If you cannot completely push in the injection button, refer to the “Questions and Answers” section, Question 7, at the end of this manual.**
- Do not inject a dose unless the Pen is primed, just before injection, or you may get too much or too little insulin.
- If you have set a dose and pushed in the injection button without a needle attached or if no insulin comes out of the needle, see the “Questions and Answers” section, Questions 1 and 2.

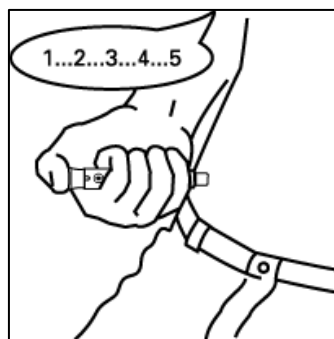
V. Injecting a Dose (Continued)

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

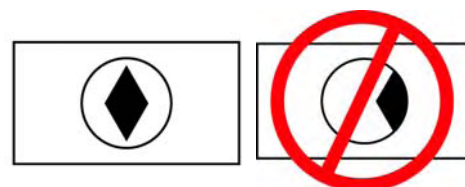
2. Insert the needle into your skin. Inject the insulin by using your thumb, if possible, to push in the injection button completely.



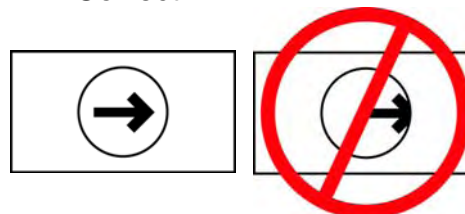
3. Keep pressing and continue to hold the injection button **firmly** while counting **slowly** to 5.



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



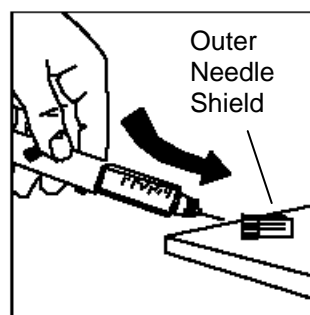
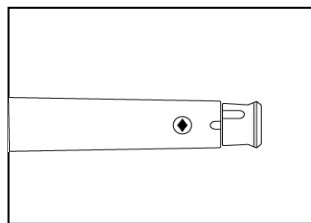
Correct



Correct

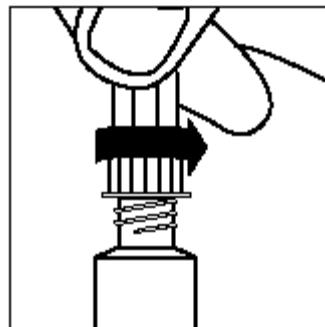
VI. Following an Injection

1. Make sure you got your full dose by checking that the injection button has been completely pushed in and you can see a diamond (◆) or an arrow (➡) in the center of the dose window. If you do not see a diamond (◆) or an arrow (➡) in the center of the dose window, you have not received your full dose. Contact your Health Care Professional for additional instructions.
2. Carefully replace the **outer needle shield** as instructed by your Health Care Professional.

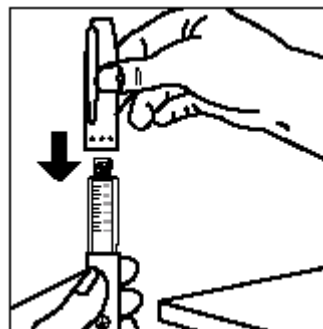


VI. Following an Injection (Continued)

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



4. Replace the cap on the Pen.



5. The Pen that you are using should **NOT** be refrigerated but should be kept at room temperature [below 86°F (30°C)] and away from direct heat and light. It should be discarded according to the time specified in the “Patient Information”, even if it still contains insulin.

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

Questions and Answers

Problem	Action
1. Dose dialed and injection button pushed in without a needle attached.	<p>To obtain an accurate dose you must:</p> <ol style="list-style-type: none"> 1) Attach a new needle. 2) Push in the injection button completely (even if a “0” is seen in the window) until a diamond (◆) or an arrow (➡) is seen in the center of the dose window. 3) Prime the Pen.
<p>2. Insulin does not come out of the needle.</p> <p>Note: You may need to prime a new pen up to six times before a stream of insulin appears.</p>	<p>To obtain an accurate dose you must:</p> <ol style="list-style-type: none"> 1) Attach a new needle. 2) Push in the injection button completely (even if a “0” is seen in the window) until a diamond (◆) or an arrow (➡) is seen in the center of the dose window. 3) Prime the Pen. See Section III. “Priming the Pen”, pages 10-13.

Questions and Answers (Continued)

Problem	Action
3. Why do I need to prime a new pen up to six times?	The first time you use a new pen, priming up to six times may be needed to see a stream of insulin come out of the tip of the needle. If you do not prime until you see a stream of insulin, you may get too much or too little insulin.
4. Wrong dose (too high or too low) dialed.	If you have not pushed in the injection button, simply turn the dose knob backward or forward to correct the dose.
5. Not sure how much insulin remains in the cartridge.	Hold the Pen with the needle end pointing down. The scale (20 units between marks) on the clear cartridge holder shows an estimate of the number of units remaining. These numbers should not be used for measuring an insulin dose.

**Questions and Answers
(Continued)**

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

**Questions and Answers
(Continued)**

Problem	Action
8. Cannot completely push in the injection button when priming the Pen or injecting a dose.	<ol style="list-style-type: none">1) Needle is not attached or is clogged.<ol style="list-style-type: none">a. Attach a new needle.b. Push in the injection button completely (even if a "0" is seen in the window) until a diamond (♦) or an arrow (➔) is seen in the center of the dose window.c. Prime the Pen.2) If you are sure insulin is coming out of the needle, push in the injection button more slowly to reduce the effort needed and maintain a constant pressure until the injection button is completely pushed in.

**For additional information call,
1-800-LILLY-RX (1-800-545-5979),
or visit our website at www.Humalog.com**

Revised XXX xx, 200x

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