Humalog® (insulin lispro injection, rDNA origin) is a human insulin analog that is synthesized by recombinant DNA technology in Escherichia coli (E. coli). Proinsulin is biochemically processed and purified from the fermentation broth. Humalog is secreted in a single homogeneous molecule of insulin, with no detectable levels of other batches that have been generally caused by the addition of copolypeptides of human insulin. Humalog has the following primary structure:

- **Primary Structure**:
  - Humalog has a primary structure of 51 amino acids, which is identical to human regular insulin.
  - The primary activity of insulin, including Humalog, is the regulation of glucose metabolism. In addition, all insulins have several anabolic effects, such as promoting protein synthesis, promoting the uptake and storage of amino acids, and promoting anabolism.

- **Absorption and Onset**: When Humalog is given subcutaneously, its t1/2 is shorter than that of human regular insulin (1 vs. 1.5 hours, respectively).

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

- **Pharmacokinetics**: Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. It is commonly used in combination with other oral antidiabetic agents or with diet and exercise in the management of Type 2 diabetes.

- **Hypoglycemia**: Hypoglycemia is a common side effect of Humalog therapy. It is important to monitor blood glucose levels regularly to prevent hypoglycemia.

- **Weight Gain**: Humalog has been shown to cause weight gain, especially when used in combination with other medications or lifestyle changes.

- **Interactions**: Humalog interacts with other medications, which may affect its effectiveness and safety.

- **Special Populations**: Humalog is generally safe and effective in special populations, such as children, elderly patients, and those with specific medical conditions.

**CLINICAL PHARMACOLOGY**

- **Pharmacodynamics**: The primary activity of insulin, including Humalog, is the regulation of glucose metabolism. In addition, all insulins have several anabolic effects, such as promoting protein synthesis, promoting the uptake and storage of amino acids, and promoting anabolism.

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**CONTRAINDICATIONS**

- **Use in Patients With Lactic Acidosis or Cardiomyopathy**: Humalog should not be used in patients with lactic acidosis or cardiomyopathy. These conditions may be exacerbated by the use of insulin.

- **Use in Patients With Renal Failure**: Humalog is not recommended for use in patients with renal failure, as it may be less effective in these patients.

- **Use in Patients With Severe Allergy:** Humalog should be used with caution in patients with severe allergy to insulin, as it may cause anaphylaxis.

**WARNINGS**

- **Hypoglycemia**: Humalog is a source of insulin that is used to treat diabetes mellitus. It is important to monitor blood glucose levels regularly to prevent hypoglycemia.

- **Weight Gain**: Humalog has been shown to cause weight gain, especially when used in combination with other medications or lifestyle changes.

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**CONSERVATIVE TREATMENTS**

- **Low-carbohydrate Diet**: A low-carbohydrate diet may be useful in reducing blood glucose levels in patients with Type 2 diabetes.

- **Exercise**: Regular exercise can help to improve insulin sensitivity and reduce blood glucose levels.

- **Weight Loss**: Weight loss can help to reduce blood glucose levels in patients with Type 2 diabetes.

**PHARMACOKINETICS**

- **Absorption and Onset**: When Humalog is given subcutaneously, its t1/2 is shorter than that of human regular insulin (1 vs. 1.5 hours, respectively).

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**REFERENCES**

- **Information on the effect of age and gender on the pharmacokinetics of Humalog is unavailable.**

**TABLE 1: Comparison of Glycemic Parameters at the End of Combined Treatment Periods**

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<tr>
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<tr>
<td>HbA1c (%)</td>
<td>8.2 ±1.4</td>
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<tr>
<td>1-Hour Postprandial</td>
<td>232.4 ±97</td>
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**FIGURE 1**: Illustration of the absorption and elimination of insulin lispro and human regular insulin after subcutaneous injection.

**Figure 2**: Comparison of serum insulin levels after subcutaneous injection of human regular insulin and Humalog in healthy male volunteers given 0.2 U/kg human regular insulin or Humalog at abdominal, deltoid, or femoral subcutaneous sites. Humalog was absorbed at a consistently faster rate than human regular insulin (U-100).

**Figure 3**: Mean blood glucose levels after subcutaneous injection of insulin lispro injection (Humalog) and human insulin in healthy male volunteers given 0.2 U/kg human regular 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.

**Table 2**: Results of a Two-Month Study in Patients with Fasting Hyperglycemia Despite Maximal Sulfonylurea Therapy

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**Figure 4**: Hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

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**Figure 5**: The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of Humalog has not been established.
Physicians should carefully evaluate information on external infusion pump in the Humalog label/package insert and in the external infusion pump's instruction manual.

PRESERVATIONS

General

Humalog® and Hypoglycemia
Humalog® is the rapid-acting insulin analog used interchangeably with human regular insulin in the treatment of diabetes mellitus in adults and children. Humalog® is intended for subcutaneous injection. It contains no preservatives. Humalog® should be inspected for visual clarity and freedom from particulate matter before administration.

Hypoglycemia

Hypoglycemia is a frequent occurrence in patients treated with Humalog® and is managed primarily with dietary intake. For patients with insulin requirements, this is determined by a combination of insulin dose, dose frequency, duration of action, and factors such as stress, exercise, and time of day. Hypoglycemia occurring during the insulin peaks of action may be managed by administering a fast-acting carbohydrate source (e.g., fruit juice or cereal) or by using a rapid source of energy (e.g., a glucose tablet or gel).

Patients with diabetes should be trained in self-assessment of plasma glucose concentrations and the symptoms and treatment of hypoglycemia. Patients should also be trained in self-assessment of plasma glucose levels and the symptoms and treatment of hypoglycemia. Patients should be informed of the risk of hypoglycemia and the importance of proper insulin storage, injection technique, and planning and adherence.

PATIENT INFORMED CONSENT

Patients should be informed of the potential risks and benefits of Humalog® and alternative therapies. Patients should be informed of the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, and periodic assessment for diabetes complications. Patients should be informed that the information insert that accompanies the drug product and the User Manual that accompanies the delivery device and re-read them each time a change in treatment occurs. Patients should be advised not to share their Pens with others.

Humalog® is not indicated for the treatment of ketosis or diabetic coma.

Onset and Action

Humalog® has a rapid onset of action and is used as a meal-time insulin. When given within 15 minutes before or immediately after a meal, Humalog® maintains its rapid onset of action and has less variability in its onset of action among individuals and at different times in the same individual. It is accompanied by a linear rise in blood glucose level within 30 to 60 minutes of injection. The time course of Humalog® action may vary in different individuals or in different times in the same individual and is dependent on the route of administration, injection site, meal size, and physical activity.

The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other factors.

As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection.

Skin and Appendages

— allergic reactions (e.g., rash, hives, angioedema, anaphylaxis).

In addition, other reactions may be expected in patients who are allergic to any of the excipients in the injection formulation.

Hypersensitivity

Hypersensitivity reactions may occur in patients treated with Humalog®. For patients with a known allergy to any of the excipients in the injection formulation, use of Humalog® is contraindicated.

Eye

— blurred vision, photophobia.

— retinopathy.

Other

— allergic reactions (see PRECAUTIONS and CONTRAINDICATIONS).

Drug Interactions

— Insulin pumps, the infusion set should be replaced and a new infusion site should be selected every 48 hours or less.

Use in an External Insulin Pump

— The patient is not required to set the rate of insulin infusion if the infusion set is properly selected and the external insulin pump is properly calibrated.

DOSAGE AND ADMINISTRATION

Storing Insulin in an External Insulin Pump

— The insulin should be 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 after its expiration date.

Approximately 30% of diabetic patients (with normoglycemia) have an increase in C-peptide concentrations. In addition, there is evidence that some patients with diabetes may have an increase in C-peptide concentrations. It is not known whether these increases are caused by the use of Humalog® or by the patient's underlying disease.

Use in an External Insulin Pump

— As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. The time course of Humalog® action may vary in different individuals or in different times in the same individual.

— To ensure that the patient understands the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, and periodic assessment for diabetes complications.

DOSAGE AND ADMINISTRATION

See PRECAUTIONS, WARNINGS.

OVERDOSAGE

In a 9-month, cross-over study of pre-pubescent children (n=60), aged 3 to 11 years, comparable glycemic control as measured by HbA1c was achieved regardless of treatment group; human regular insulin 30 to 45 minutes before meals resulted in HbA1c levels of 8.7% and Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all three treatment groups. Patients treated with human regular insulin may be required to improve accuracy in dosing in pediatric patients, a diluent may be used. If the diluent is used, the patient should be informed of the potential risks and benefits of Humalog® and alternative therapies.

ADVERSE REACTIONS

Clinical studies comparing Humalog® with human regular insulin resulted in a difference in frequency of adverse events between the two therapies.

Advise patients to inform their health care professionals about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, and periodic assessment for diabetes complications.

Insulin pumps should be rotated every 48 hours or less. Humalog® in the external insulin pump should not be exposed to temperatures above 37°C (98.6°F). When used in an external insulin pump, the infusion set should be replaced and a new infusion site should be selected every 48 hours or less.
**INFORMATION FOR THE PATIENT CARTRIDGE**

**HUMALOG® INSULIN LISPRO INJECTION (rDNA ORIGIN) 100 UNITS PER ML (U-100)**

**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 ... do not use a Humalog cartridge if it has been frozen.

Do not use Humalog after the expiration date stamped on the label.

**HUMALOG® INSULIN LISPRO INJECTION (rDNA ORIGIN)**

**100 UNITS PER ML (U-100)**

**Description**

Humalog (insulin lispro [rDNA origin]) is made by a special non-disease-producing laboratory strain of Escherichia coli bacteria that has been genetically altered by the addition of the gene for this human insulin analog. Humalog consists of zinc-insulin lispro crystals dissolved in a clear fluid. Humalog is a sterile solution and is for subcutaneous injection. It should not be used intramuscularly. The concentration of Humalog is 100 units/mL (U-100). Humalog starts lowering blood glucose more quickly and has a shorter duration of action compared to regular human insulin. This means that your dose of Humalog should be given within 15 minutes before or immediately after eating a meal (regular insulin works best when given 30 to 60 minutes before eating a meal). The short duration of action of Humalog means that if you have type 1 diabetes, you need to use a longer-acting insulin to give the best glucose control (except when using an external insulin pump). If you have type 2 diabetes, Humalog may be used within a longer-acting insulin when using an combination therapy with sulfonylurea agents. The time course of Humalog action, like that of other insulins, may vary in different individuals at different times in the same individual, based on dose, site of injection, blood supply, temperature, and physical activity.

**WARNINGs**

This Lilly human insulin analog is different from other insulins because it has a rapid onset and shorter duration of action. The rapid onset of action may mean that you should take your dose of HUMALOG® (insulin lispro injection, rDNA origin) within 15 minutes before or immediately after eating a meal. The short duration of action of HUMALOG® means that if you have type 1 diabetes, you also need to use a longer-acting insulin to give the best glucose control (except when using an external insulin pump). If you have type 2 diabetes, HUMALOG® may be used without a longer-acting insulin when using combination therapy with sulfonylurea agents. The time course of Humalog action, like that of other insulins, may vary in different individuals at different times in the same individual, based on dose, site of injection, blood supply, temperature, and physical activity.

**Identification**

Cartridges of insulin lispro injection (rDNA origin), by Eli Lilly and Company, have the trademark Humalog. Your doctor has prescribed the type of insulin that is best for you.

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

**3 ML CARTRIDGE**

For use in Eli Lilly and Company's HumaPen® MEMORI™ and HumaPen® LUXURATM HD1 insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3 mL insulin delivery device (reusable insulin Pen), Disetronic® 3 D-TRON® or D-TRON® plus insulin pumps.

**PREPARING FOR AN INJECTION USING REUSABLE INSULIN PEN OR EXTERNAL INSULIN PUMP**

1. Inspect the appearance of Humalog solution before you insert the cartridge into the reusable insulin Pen or external insulin pump. Humalog should look clear and colorless. Do not use Humalog if it appears cloudy, thickened, colored, or if solid particles are visible. Once the cartridge is in use, inspect the insulin in the insulin Pen before each injection. When using a Humalog cartridge in an external insulin pump, inspect the cartridge before inserting it in the external insulin pump and periodically during use.

2. Use in Reusable Insulin Pen — Follow the reusable insulin Pen manufacturer's instructions carefully for loading the cartridge into the insulin Pen and for use of the insulin Pen.

a. Use an alcohol swab to wipe the exposed rubber surface on the metal cap end of the cartridge.

b. Follow the insulin needle manufacturer's instructions for attaching and changing the needle.

3. Use in an External Insulin Pump — Follow the external insulin pump manufacturer's instructions carefully for use of Humalog 3 mL cartridges in the Disetronic® 3 D-TRON®, or D-TRON® plus insulin pump.

**GENERAL INSTRUCTIONS FOR USE IN A Reusable Insulin Pen**

1. Wash your hands.

2. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the previous injection site. The usual sites of injection are abdomen, thighs, and arms.

3. Cleanse the skin with alcohol where the injection is to be made.

4. With one hand, stabilize the skin by spreading it or pinching up a large area. Do not use if it appears cloudy, thickened, or slightly colored, or if solid particles are visible. If you note anything unusual in its appearance or notice your insulin requirements changing markedly, consult your doctor.

**Storage**

When used in a Reusable Insulin Pen

Not in-use (unopened): Unopened Humalog cartridges should be stored in a refrigerator but not in the freezer. Do not use a Humalog cartridge if it has been frozen.

In-use (unopened): Humalog cartridges in-use should NOT be refrigerated but should be kept at room temperature (below 86°F [30°C]) away from direct heat and light. Humalog cartridge that you are using must be discarded 28 days after the first use.

Do not use Humalog after the expiration date stamped on the label.

When used in an External Insulin Pump

Infusion sets (tubing and catheters) and D-TRON® or D-TRON® plus cartridge adapter should be discarded every 48 hours or less. Humalog in an external insulin pump should not be exposed to temperatures above 98°F (37°C) such as in sauna or hot tub, hot showers, direct sunlight, or radiant heater.

A Humalog 3 mL cartridge used in the D-TRON® or D-TRON® plus pump should be discarded after 7 days, even if it still contains Humalog.

**INSTRUCTIONS FOR USE**

REUSABLE INSULIN PENS, EXTERNAL INSULIN PUMPS, INFUSION SETS, CARTRIDGES, OR NEEDLES.

NEVER SHARE INSULIN PENS, EXTERNAL INSULIN PUMPS, INFUSION SETS, CARTRIDGES, OR NEEDLES.

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NEVER SHARE INSULIN PENS, EXTERNAL INSULIN PUMPS, INFUSION SETS, CARTRIDGES, OR NEEDLES.
Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin. Exercise may lower your body's need for insulin products during and for some time after the physical activity. Exercise may also speed up the effect of a dose of Humalog, especially if the exercise involves the area of injection site. Discuss with your doctor how you should adjust your regimen to accommodate exercise.

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

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

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

Hypoglycemia (Low Blood Sugar)
Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- sweating
- drowsiness
- dizziness
- sleep disturbances
- anxiety
- memory loss
- shared speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness

Therefore, it is important that assistance be obtained immediately. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, changing insulin preparations, or intensified control (3 or more injections per day) of diabetes. A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin. Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia. Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious may require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility. You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

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

Hyperglycemia and Diabetic Ketoacidosis (DKA)

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

1. Omitting your insulin or taking less than the doctor has prescribed.
2. Eating significantly more than your meal plan suggests.
3. Developing a fever, infection, or other significant stressful situation.
4. Arteriosclerosis with type 1 or insulin-dependent diabetes, prolonged hypoglycemia can result in DKA. The first symptoms of DKA usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath. With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach 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 lipodystrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

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

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

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

DIABETES FORECAST is a magazine designed especially for people with diabetes and their families. It is available by subscription from the American Diabetes Association (ADA), P.O. Box 363, Mt. Morris, IL 60545-0363, 1-800-DIABETES (1-800-342-2383).

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

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

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