

AUSTRALIAN PRODUCT INFORMATION

HUMALOG® [INSULIN LISPRO (RBE)] 10-ML VIAL

HUMALOG® CARTRIDGE [INSULIN LISPRO (RBE)] 3 ML

HUMALOG® KWIKPEN® [INSULIN LISPRO (RBE)] 3 ML

**HUMALOG® MIX25® CARTRIDGE [25% INSULIN LISPRO (RBE) AND
75% INSULIN LISPRO (RBE) PROTAMINE SUSPENSION] 3 ML**

**HUMALOG® MIX25® KWIKPEN® [25% INSULIN LISPRO (RBE) AND
75% INSULIN LISPRO (RBE) PROTAMINE SUSPENSION] 3 ML**

**HUMALOG® MIX50® CARTRIDGE [50% INSULIN LISPRO (RBE) AND
50% INSULIN LISPRO (RBE) PROTAMINE SUSPENSION] 3 ML**

**HUMALOG® MIX50® KWIKPEN® [50% INSULIN LISPRO (RBE) AND
50% INSULIN LISPRO (RBE) PROTAMINE SUSPENSION] 3 ML**

1. NAME OF THE MEDICINE

Insulin lispro (rbe)

2 AND 3. QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

The HUMALOG range consists of three presentations:

HUMALOG - Insulin lispro solution [recombinant DNA origin] is an aqueous solution of insulin lispro ([Lys (B28), Pro (B29)] human insulin analogue, adjusted to pH 7.0 to 7.8. It also contains metacresol, glycerol, dibasic sodium phosphate heptahydrate, zinc oxide and water for injection. Hydrochloric acid and sodium hydroxide may be used to adjust pH.

HUMALOG is available as a clear, colourless solution for parenteral administration in a concentration of 100 units/mL in 10-mL vials, 3-mL cartridges and 3-mL prefilled insulin delivery devices (HUMALOG KwikPen).

HUMALOG MIX25 – 25% insulin lispro and 75% insulin lispro protamine suspension (NPL) [recombinant DNA origin] is a mixture of insulin lispro, a rapid-acting blood glucose lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose lowering agent, adjusted to pH 7.0 to 7.8.

HUMALOG MIX25 is available as a white suspension for parenteral administration in a concentration of 100 units/mL in 3 mL cartridges and 3 mL prefilled insulin delivery devices (HUMALOG MIX25 KwikPen).

HUMALOG MIX50 –50% insulin lispro and 50% insulin lispro protamine suspension (NPL) [recombinant DNA origin] is a mixture of insulin lispro, a rapid-acting blood glucose lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose lowering agent, adjusted to pH 7.0 to 7.8.

HUMALOG MIX50 is available as a white suspension for parenteral administration in a concentration of 100 units/mL in 3-mL cartridges and 3-mL prefilled insulin delivery devices (HUMALOG MIX50 KwikPen).

HUMALOG MIX25 and HUMALOG MIX50 also contain metacresol, phenol, glycerol, dibasic sodium phosphate heptahydrate, protamine sulfate, zinc oxide and water for injection. Hydrochloric acid and sodium hydroxide may be used to adjust pH.

HUMALOG is a Lilly human insulin analogue. It differs from other insulins because it has a unique structure, a very quick onset of action and a shorter duration of activity. HUMALOG MIX25 and HUMALOG MIX50 combine the quick onset of action of HUMALOG with an extended duration of activity attributable to the intermediate acting component of the mixture. HUMALOG, HUMALOG MIX25 and HUMALOG MIX50 should be given immediately (up to 15 minutes) before a meal. When necessary, HUMALOG can be given soon after meals (within 20 minutes of the start of a meal). The safety and efficacy of HUMALOG MIX25 and HUMALOG MIX50 given after a meal has not been established.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of patients with Type 1 (IDDM) and Type 2 (NIDDM) diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Compared to regular insulin, HUMALOG takes effect more rapidly and has a shorter duration of activity (2 to 5 hours).

Adults

In adults, HUMALOG, HUMALOG MIX25 and HUMALOG MIX50 can be given immediately (up to 15 minutes before a meal). When necessary, HUMALOG can be given soon after meals (within 20 minutes of the start of the meal). The safety and efficacy of HUMALOG MIX25 and HUMALOG MIX50 given after a meal has not been established.

In patients with Type 2 diabetes HUMALOG may be administered in combination therapy with oral sulfonylurea agents.

Children

In clinical studies involving children and adolescents (ages 3 to 19 years), HUMALOG has been shown to be safe, effective and well-tolerated.

HUMALOG can be given immediately (up to 15 minutes before a meal). When necessary, HUMALOG can be given soon after meals (within 20 minutes of the start of the meal). The safety and efficacy of HUMALOG MIX25 and HUMALOG MIX50 in children has not been established.

General

During changes to a patient's insulin regimen, increase the frequency of glucose monitoring.

HUMALOG should be given by subcutaneous injection. It may also be administered intravenously.

HUMALOG MIX25 and HUMALOG MIX50 should only be given by subcutaneous injection. It should not be administered intravenously. The safety and efficacy of HUMALOG MIX25 and HUMALOG MIX50 given after a meal has not been established. The rapid onset and early peak activity of HUMALOG is observed following the subcutaneous administration of HUMALOG MIX25 and HUMALOG MIX50. The duration of action of the insulin lispro protamine suspension (NPL) component of HUMALOG MIX25 and HUMALOG MIX50 is similar to that of basal insulin NPH.

Subcutaneous administration should be in the abdomen or thighs. The injection sites should be rotated so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and localised cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localised cutaneous amyloidosis.

Care should be taken when injecting HUMALOG MIX25 and HUMALOG MIX50 to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged.

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 HUMALOG is dependent on dose, site of injection, blood supply, temperature and physical activity.

HUMALOG should not be considered as clinically equivalent to human insulin as the time to onset and time course of action are different compared with regular human insulin (see **5 Pharmacological Properties**).

As HUMALOG has a time activity profile that is different from other insulins, patients previously stabilised on other insulin products should be titrated cautiously with HUMALOG, under medical supervision (see **4.4 Special warnings and precautions for use**).

HUMALOG may be administered in combination regimens with HUMULIN NPH.

HUMALOG has been mixed with HUMULIN NPH. In normal volunteers, mixing HUMALOG with HUMULIN NPH immediately prior to subcutaneous injection does not affect the rapid absorption of HUMALOG, compared to administration of the two insulins as separate injections. There is a lack of systematic experience, in diabetic patients, concerning the mixing of HUMALOG with other insulins. HUMALOG should not be mixed with any other animal or human insulin preparations. HUMALOG MIX25 or HUMALOG MIX50 should not be mixed with other insulins.

Instructions for Use/Handling

To prevent the possible transmission of disease, each HUMALOG KwikPen or cartridge must be used by one patient only, even if the needle is changed.

HUMALOG should be used as a multiuse vial in individual patients only.

HUMALOG – Use in Continuous Subcutaneous Infusion Pumps

The compatibility of HUMALOG has been studied in MiniMed and Accu-check (formerly Disetronic) insulin infusion pump systems (see **5.1 Pharmacodynamic properties, Clinical trials**). HUMALOG should be used in pumps according to the manufacturer's directions. The correct reservoir and catheter for the pump should be used and the entire infusion set (including the syringe and its contents) should be changed every 48 hours. When used with an insulin infusion pump, HUMALOG should not be mixed with any other insulin.

Patients should ensure they have access to an alternative device at all times in case of pump failure (see **4.4 Special warnings and precautions for use**).

HUMALOG MIX 25 and HUMALOG MIX 50 should not be used in pumps.

HUMALOG MIX25 and HUMALOG MIX50 Cartridges

Cartridges should be rolled between the palms 10 times. Holding the cartridge by one end, invert it 180° slowly 10 times to allow the glass bead to travel the full length of the cartridge with each inversion. Cartridges should not be shaken vigorously as this may cause frothing which may interfere with the correct measurement of the dose. The insulin should look uniformly cloudy after mixing. If it does not, the above steps should be repeated until the contents are mixed. Cartridges of insulin should be examined frequently and should not be used if the insulin substance (the white material) remains visibly separated from the liquid after mixing. Cartridges of insulin should not be used if there are clumps in the insulin after mixing or if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance.

HUMALOG MIX25 and MIX50 KwikPens

KwikPen prefilled insulin pen delivery devices should be rolled between the palms 10 times. Holding the device by one end, invert it 180° slowly 10 times to allow the glass bead to travel the full length of the cartridge with each inversion. The devices should not be shaken vigorously as this may cause frothing which may interfere with the correct measurement of the dose. The insulin should look uniformly cloudy after mixing. If it does not, the above steps should be repeated until the contents are mixed. KwikPen prefilled insulin pen delivery devices should be examined frequently and should not be used if the insulin substance (the white material) remains visibly separated from the liquid after mixing. KwikPen prefilled insulin pen delivery devices should not be used if there are clumps in the insulin after mixing or if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance. For instructions on how to administer the insulin, refer to the manufacturer's instructions for the insulin pen delivery device.

4.3 CONTRAINDICATIONS

Hypoglycaemia.

Hypersensitivity to insulin lispro or one of its excipients.

HUMALOG MIX25 and HUMALOG MIX50 should not be given intravenously.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Any change in an insulin or human insulin analogue regimen should be made cautiously and only under medical supervision with increased frequency of glucose monitoring. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal, human, human insulin analogue) and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

The shorter acting HUMALOG should be drawn into the syringe first, to prevent contamination of the vial by the longer acting insulin. Mixing of the insulins ahead of time or just before the injection should be on advice of the doctor. However, a consistent routine must be followed.

Patients using any of the HUMALOG range of insulins may require a change in dosage from that used with their usual insulins. If dosage adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Patients whose glycaemic control is greatly improved, e.g. by flexible insulin therapy, may lose some or all of the warning symptoms of hypoglycaemia and should be advised accordingly.

A few patients who have experienced hypoglycaemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

Some studies with human insulin have shown increased levels of circulating insulin in patients with renal and/or hepatic dysfunction. Careful glucose monitoring and dose adjustments of insulins, including HUMALOG, may be necessary.

Thiazolidinediones (TZDs) in combination with insulin are associated with an increased risk of oedema and heart failure; especially in patients with underlying cardiac disease.

Insulin requirements may be increased during illness or emotional disturbances.

Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet.

HUMALOG MIX25 or HUMALOG MIX50 should under no circumstances be administered intravenously. Mixing of HUMALOG MIX25 or HUMALOG MIX50 with other insulins has not been studied. Therefore, HUMALOG MIX25 or HUMALOG MIX50 should not be mixed with other insulins.

Injection technique

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after

the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Subcutaneous Insulin Infusion Pumps

Malfunction of the insulin pump or infusion set (including pump malfunction, infusion set occlusion, leakage, disconnection or kinking) or insulin degradation can rapidly lead to hyperglycaemia and ketosis. Prompt identification and correction of the cause of hyperglycaemia or ketosis is necessary and interim subcutaneous injections with HUMALOG may be required. Patients using continuous subcutaneous infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy and device available in case of pump failure (see **4.2 Dose and method of administration**).

Use in hepatic impairment

Insulin requirements may be reduced in the presence of hepatic impairment.

Use in renal impairment

Insulin requirements may be reduced in the presence of renal impairment.

Use in the Elderly

No data available

Paediatric Use

The safety and efficacy of HUMALOG MIX25 and HUMALOG MIX50 in patients less than 18 years of age has not been established.

Effects on Laboratory Tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The physician should be consulted when using other medication in addition to insulin lispro (see **4.4 Special warnings and precautions for use**).

Insulin requirements may be increased by drugs with hyperglycaemic activity, such as oral contraceptives, corticosteroids, thyroid replacement therapy, isoniazid, phenothiazines, danazol or beta-2 stimulants (such as salbutamol, terbutaline).

Insulin requirements may be reduced in the presence of drugs with hypoglycaemic activity, such as oral hypoglycaemics, salicylates (for example, aspirin), sulphonamides, certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme inhibitors (captopril and enalapril), angiotensin II receptor blockers, beta blockers, octreotide and alcohol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No effects on male or female fertility have been observed in rats dosed subcutaneously with insulin lispro at dose levels up to 20 U/kg/day.

Use in pregnancy

Pregnancy Category A

HUMALOG can be used during pregnancy. There is a large body of data which suggests that the use of HUMALOG during pregnancy is beneficial, and as safe as other forms of insulin therapy.

In a retrospective cohort study, the medical records of 496 women with Type 1 or Type 2 diabetes treated with HUMALOG for at least 1 month before conception and during at least the first trimester of pregnancy were reviewed to determine the rate of major congenital anomalies in their offspring. Outcomes of 533 pregnancies (542 offspring) showed the incidence of major congenital anomalies in the offspring was 5.4% (95% CI: 3.45%, 7.44%), consistent with previously published results for the offspring of women with type 1 and type 2 pregestational diabetes.

The safety and efficacy of HUMALOG MIX25 and HUMALOG MIX50 has not been established during pregnancy.

It is essential to maintain good control of the insulin-treated patient (insulin-dependent or gestational diabetes) throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

A reproductive study in rats showed no adverse effects on pregnancy or foetal development when insulin lispro was injected subcutaneously once daily at doses up to 20 U/kg. Teratogenic potential has not been adequately assessed in rabbits, although one study showed no embryotoxic or teratogenic activity at subcutaneous doses up to 0.75 U/kg/day. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in lactation

Patients with diabetes who are lactating may require adjustments in insulin dose, diet or both. It is not known if insulin lispro is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The patient's ability to concentrate and to react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia while driving, this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The preclinical safety profile indicates that HUMALOG is safe in the chronic treatment of diabetes in humans. The safety profile of HUMALOG has been assessed in a series of preclinical studies. In in vitro tests, including binding to insulin receptor sites and effects on growing cells, HUMALOG behaved in a manner that closely resembled human insulin. Toxicology studies produced no significant toxicity findings. Most importantly, and like human insulin, HUMALOG did not produce proliferative effects or tumours in organs and tissues when given at very high subcutaneous doses in chronic toxicity tests.

Hypoglycaemia

Hypoglycaemia is the most frequent undesirable effect of insulin therapy. Severe hypoglycaemia may lead to loss of consciousness and, in extreme cases, death. The clinical studies on HUMALOG showed no difference between the frequency of symptomatic hypoglycaemia or the frequency of hypoglycaemic coma when compared to HUMULIN R; however, the studies did show a consistent, but not always significant, reduction of postprandial glycaemic excursion in patients using HUMALOG.

Allergic Reactions

Local allergy in patients occasionally occurs as redness, swelling and itching at the site of insulin injection. This condition usually resolves 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. Systemic allergy, less common but potentially more serious, is a generalised allergy to insulin. It may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse or sweating. Severe cases of generalised allergy may be life-threatening.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipoatrophy or lipohypertrophy. A change in injection technique may help alleviate the problem.

Spontaneous Data

Cases of oedema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy (see **4.4 Special warnings and precautions for use**).

Lipodystrophy and localised cutaneous amyloidosis at the injection site have occurred. Hyperglycaemia has been reported with repeated insulin injections into areas of lipodystrophy or localised cutaneous amyloidosis; hypoglycaemia has been reported with a sudden change to an unaffected injection site (see section **4.4 Special warnings and precautions for use**).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

Insulins have no specific overdose definitions because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability and other metabolic processes. Hypoglycaemia may occur as a result of an excess of insulin or insulin analogue relative to food intake and energy expenditure.

Hypoglycaemia may be associated with listlessness, confusion, palpitations, headache, sweating and vomiting.

Mild hypoglycaemic episodes will respond to oral administration of glucose or other sugar or saccharated products.

Correction of moderately severe hypoglycaemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously.

If the patient is comatose, glucagon should be administered intramuscularly or subcutaneously. However, glucose solution must be given intravenously if glucagon is not available or if the patient fails to respond to glucagon. The patient should be given a meal as soon as consciousness is recovered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The unique structure of HUMALOG, compared to regular human insulin, results in a faster rate of absorption from subcutaneous sites of injection, a more rapid effect and a shorter duration of action, more closely mimicking the normal physiological response.

HUMALOG has a very rapid onset of action, allowing it to be given immediately before a meal, compared to regular insulin, which should be given 30 minutes before a meal. In initial clinical pharmacology studies, the onset of action of HUMALOG was seen within 15 minutes of administration, while onset of action for regular insulin was 30 to 45 minutes following administration. Serum insulin levels peaked earlier with HUMALOG, corresponding to an earlier peak action of HUMALOG (approximately 1 hour) as compared to regular insulin (2 to 3 hours). The pharmacokinetics of HUMALOG translated into a shorter duration of activity when compared to regular insulin, approximately 3.5 to 4.5 hours for HUMALOG as compared with 5.5 to 7.5 hours for regular insulin.

Results of a glucose clamp study in healthy volunteers showed that the absorption and activity profiles of insulin lispro protamine suspension (NPL) are similar to those of human insulin isophane suspension (NPH). The pharmacokinetic and pharmacodynamic profiles of insulin lispro/ insulin lispro protamine suspension (NPL) mixtures were investigated in a separate glucose clamp study. The rapid activity of insulin lispro was maintained within each

mixture. In addition, each mixture demonstrated a distinct pharmacokinetic and glucodynamic profile.

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, body temperature and physical activity. The primary activity of HUMALOG is the regulation of glucose metabolism.

In addition, insulins have several anabolic and anti-catabolic actions on a variety of different tissues. 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.

Clinical trials

Eight pivotal studies were designed to evaluate the use of HUMALOG as a mealtime insulin using postprandial glucose control as the primary efficacy objective. These studies were designed to incorporate men and women of many racial/ethnic heritages and cultural dietary patterns aged 12 to 85 with new or previously treated Type 1 or Type 2 diabetes mellitus. In these trials, 2,247 patients received HUMALOG.

Four global, multicentre, clinical studies of HUMALOG (studies IOAA - IOAD) were designed to incorporate Type 1 and Type 2 patients who were already receiving insulin therapy and who had been treated with human insulin for at least 2 months prior to study entry. All four were 1-year, open-label, randomised, parallel studies using HUMULIN R in a multiple daily injection, basal-bolus therapeutic regimen as the active comparator (see Table 1).

Four global, multicentre, clinical studies of HUMALOG (studies IOAE - IOAH) were conducted to incorporate Type 1 and Type 2 patients who had never received insulin, to evaluate antibody formation in patients not previously treated with insulin, and to have larger studies of both Type 1 and 2 patients previously treated with insulin (see Table 1).

The studies in new Type 1 and Type 2 patients, IOAE and IOAF, were 1-year, open-label, randomised, parallel, studies using HUMULIN R as the active comparator. The choice of basal insulin was at the discretion of the investigator, either HUMULIN NPH or HUMULIN UL, and once chosen was the basal insulin for the entire study. The study design was identical to the earlier studies, IOAA - IOAD.

Studies IOAG and IOAH were 6-month, open-label, randomised, crossover studies in Type 1 and Type 2 patients who were currently being treated with insulin and had been using human insulin for at least the previous 2 months. HUMULIN R was the active comparator. The choice of basal insulin was at the discretion of the investigator, either HUMULIN NPH or HUMULIN UL, and once chosen was the basal insulin for the entire study. The power of the crossover design, with each patient serving as his or her own control, and the large patient numbers allowed these two studies to provide the major conclusions (consistent with the conclusions of the first six studies) regarding the efficacy of HUMALOG on reduction of the postprandial glucose excursion in patients with diabetes. In addition, study IOAG demonstrated a significant reduction in the rate of hypoglycaemia overall as well as demonstrating significant reduction in nocturnal hypoglycaemia in patients receiving HUMALOG.

In all of the studies there were no clinically significant safety issues with HUMALOG. There was no evidence of increased immunogenicity of HUMALOG compared to HUMULIN R. Further studies are continuing on the immunogenicity of HUMALOG.

In the clinical trials of HUMALOG, approximately one-half to two-thirds of Type 1 patients and approximately one-third of Type 2 patients had their basal insulin in the morning. More than 90% of the patients having a morning dose of basal insulin had it mixed with their breakfast dose of HUMALOG.

Table 1.

| Study | Number of Patients ^a | 2-Hour Excursion ^b | | HbA _{1c} ^c | |
|-------|---------------------------------|-------------------------------|-------------|--------------------------------|-------------|
| | | HUMALOG | HUMULIN R | HUMALOG | HUMULIN R |
| IOAA | 167 | 0.07 ± 4.87 ** | 2.92 ± 4.28 | 8.14 ± 1.30 + | 8.38 ± 1.37 |
| IOAB | 145 | 1.04 ± 3.66 * | 2.49 ± 3.94 | 8.00 ± 1.21 | 8.20 ± 1.64 |
| IOAC | 169 | 1.99 ± 5.08 | 2.75 ± 4.64 | 8.08 ± 1.43 | 8.22 ± 1.44 |
| IOAD | 150 | 1.74 ± 3.76 * | 2.84 ± 3.25 | 8.38 ± 1.52 | 8.50 ± 1.73 |
| IOAE | 98 | 1.31 ± 4.29 | 2.78 ± 4.37 | 7.77 ± 2.24 | 7.84 ± 2.35 |
| IOAF | 375 | 2.38 ± 3.64 | 2.83 ± 2.94 | 8.32 ± 1.57 | 8.08 ± 1.54 |
| IOAG | 1008 | -0.51 ± 4.88 ** | 1.52 ± 5.05 | 8.24 ± 1.49 | 8.17 ± 1.46 |
| IOAH | 722 | 1.40 ± 3.67 ** | 2.97 ± 3.73 | 8.18 ± 1.30 | 8.18 ± 1.38 |

Abbreviations: HbA_{1c} = haemoglobin A_{1c}.

^a Number of patients enrolled.

^b Blood Glucose Excursion (mmol/L), Endpoint values, means ± standard deviation.

^c Haemoglobin A_{1c} (%), Endpoint values, means ± standard deviation.

* p < 0.025 ** p < 0.001 + p = 0.031

Clinical studies have demonstrated significant improvement in postprandial glucose excursions without producing delayed postprandial hyperglycaemia and without an adverse effect on overall control as measured by haemoglobin A_{1c}. Therapy with HUMALOG was also associated with no adverse impact on hypoglycaemia, and, in fact, in the large studies with Type 1 patients (those most at risk of hypoglycaemia) there was a reduction in the rate of hypoglycaemia overall and a reduction in nocturnal hypoglycaemia. Across all of the studies there were no significant safety issues.

HUMALOG is superior to regular human insulin in those measures that reflect rapid onset and shorter duration of action. Early studies showed no significant difference in overall glycaemic control, as measured by haemoglobin A_{1c}, between HUMALOG and regular human insulin, either in patients established on insulin or in newly diagnosed patients. Haemoglobin A_{1c} is improved with HUMALOG by varying the basal regimen, to compensate for preprandial hyperglycaemia and to make use of the reduced postprandial blood glucose levels provided by HUMALOG.

When used in MiniMed 507 or 507c subcutaneous infusion pumps, treatment with HUMALOG has been shown to result in statistically significant lower haemoglobin A_{1c} levels compared to soluble insulin. It is not known if this is a clinically significant difference. Study IOEB was a 6-month, open-label, crossover study of Type 1 patients who were randomised to receive HUMALOG or regular human insulin for 12 weeks using the MiniMed 506 insulin infusion pump. After 12 weeks the patients were crossed over to the alternative treatment. All patients had used insulin infusion devices for at least 12 months prior to randomisation.

Bolus doses of regular human insulin were given 15 to 30 minutes before meals and HUMALOG was given 0 to 5 minutes before meals. The primary efficacy variable for this study was the standard deviation in blood glucose values, which was shown to be smaller on HUMALOG. Haemoglobin A1c levels were determined at the end of the run-in phase, at 12-weeks and at the end of the study.

Study IOCR had a similar study design as study IOEB, except it was an 8-month study. The primary efficacy variable for this study was postprandial blood glucose values. Haemoglobin A1c levels were determined at baseline, at 16-weeks and at the end of the study.

Study IOEQ had a similar study design as study IOEB, however bolus doses of regular human insulin or HUMALOG were given immediately before meal onset. The primary efficacy variable for this study was postprandial blood glucose values. Haemoglobin A1c levels were determined at baseline, at 12 weeks and at the end of the study.

Studies IOEB and IOCR used pumps that were not registered in Australia. Study IOEQ used various pump models. Of these, the MiniMed 507 pump is registered in Australia.

Table 2. Summary of CSII Studies with Reported HbA1c Levels

| Study | Number enrolled | Duration ^a (months) | Baseline HbA1c (%) | L - R ^b (%) | p-value | Brand and model of pumps used |
|-------|-----------------|--------------------------------|--------------------|------------------------|---------|--|
| IOCR | 113 | 4 | 7.24 | -0.13 | 0.017 | Disetronic H-TRON V100 or MiniMed models unspecified |
| IOEB | 39 | 3 | 7.81 | -0.76 | 0.001 | MiniMed 506 |
| IOEQ | 58 | 3 | 7.74 | -0.24 | 0.004 | MiniMed (504, 504-s, 506 or 507) |

^a duration of each treatment period; ^b difference in HbA1c between end of insulin lispro (L) and end of regular insulin (R) treatment.

In patients with Type 2 diabetes on maximum doses of sulfonylurea agents, the addition of HUMALOG resulted in an improvement in haemoglobin A1c compared to patients continuing on sulfonylurea therapy alone. Study IOCE was a 2-month randomised, open-label comparative study of HUMALOG, sulfonylurea and insulin NPH combinations. In this study, haemoglobin A1c levels were reduced by 1.6% with the combination of HUMALOG and sulfonylurea, when compared to baseline, in patients with fasting hyperglycaemia despite maximal doses of sulfonylurea.

5.2 PHARMACOKINETIC PROPERTIES

Refer to **5.1 Pharmacodynamic properties**.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There was no evidence of any genotoxic activity in a range of assays for gene mutations, chromosomal effects and DNA damage.

Carcinogenicity

Carcinogenicity studies of insulin lispro have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to **2 and 3 Qualitative and quantitative composition and Pharmaceutical Form.**

6.2 INCOMPATIBILITIES

HUMALOG should not be mixed with any other animal or human insulin preparations. HUMALOG MIX25 or HUMALOG MIX50 should not be mixed with other insulins. Refer to **4.2 Dose and method of administration.**

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

HUMALOG preparations should be stored in a refrigerator between 2°C and 8°C. They should not be frozen or exposed to excessive heat or sunlight.

HUMALOG vials, cartridges and KwikPen prefilled pen delivery devices can be kept at ambient temperature below 30°C and away from direct heat and light for 28 days while in use. HUMALOG MIX25 and HUMALOG MIX50 cartridges can be kept at ambient temperature below 30°C and away from direct heat and light for 28 days while in use. The reusable cartridge pen combination should not be refrigerated.

6.5 NATURE AND CONTENTS OF CONTAINER

HUMALOG [100 U/mL of insulin lispro (rbe)] is supplied in:

- 10-mL rubber-stoppered vials.
- 3-mL cartridges for use in the HumaPen (5 cartridges per pack).
- KwikPen prefilled insulin delivery device containing a 3-mL cartridge (5 per pack).

HUMALOG MIX25 (100 U/mL of 25% insulin lispro (rbe) and 75% insulin lispro (rbe) protamine suspension) is supplied in:

- 3-mL cartridges for use in the HumaPen (5 cartridges per pack).
- KwikPen prefilled insulin delivery device containing a 3-mL cartridge (5 per pack).

HUMALOG MIX50 (100 U/mL of 50% insulin lispro (rbe) and 50% insulin lispro (rbe) protamine suspension) is supplied in:

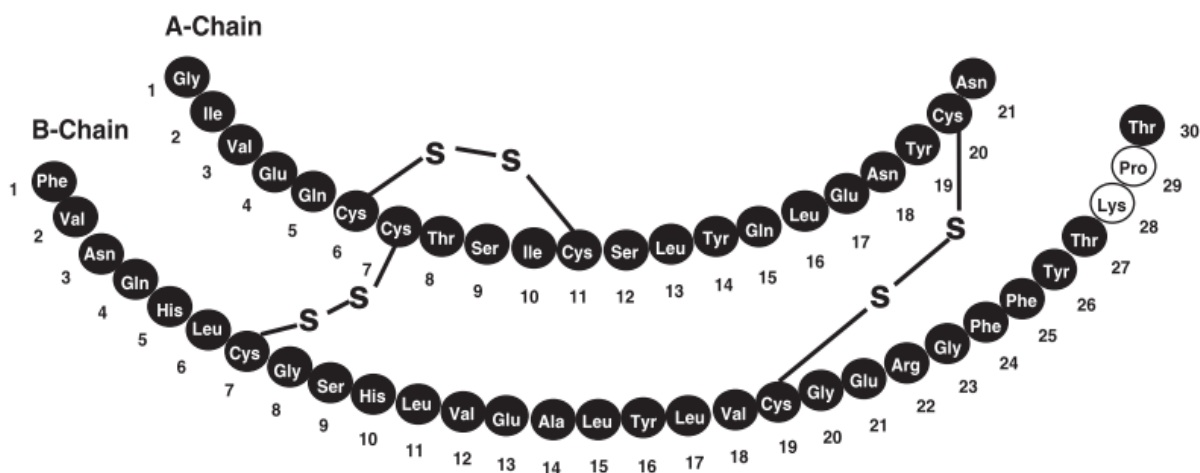
- 3-mL cartridges for use in the HumaPen (5 cartridges per pack).
- KwikPen prefilled insulin delivery device containing a 3-mL cartridge (5 per pack).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

133107-64-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

8. SPONSOR

Eli Lilly Australia Pty. Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA
1800 454 559

9. DATE OF FIRST APPROVAL

13 June 1996.

10. DATE OF REVISION

21 September 2023

SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|-----------------|----------------------------|
| 8 | Sponsor address update |

HUMALOG® is a registered trademark of Eli Lilly and Company.