PA002ITIN01

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Insulin Lispro Biphasic Injection I.P. (25% Insulin Lispro and 75% Insulin Lispro Protamine Suspension) Injection (r-DNA origin)

Humalog Mix25® KwikPen™

100IU/mL in Prefilled pen 3mL
[Monocomponent Insulin Lispro, recombinant DNA origin]

Insulin Lispro Biphasic Injection I.P. (50% Insulin Lispro and 50% Insulin Lispro Protamine Suspension) Injection (r-DNA origin)

Humalog® Mix50™ KwikPen™

100IU/mL in Prefilled pen 3mL
[Monocomponent Insulin Lispro, recombinant DNA origin]

Lilly

NAME OF THE MEDICINAL PRODUCT

Humalog Mix25® KwikPen™ 100 IU/mL suspension for injection.
Humalog® Mix50™ KwikPen™ 100 IU/mL suspension for injection.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of 25 % Insulin lispro and 75 % Insulin lispro Protamine Suspension contains : 100 IU (equivalent to 3.5 mg) Insulin lispro I.P. (r-DNA origin) as active ingredient, 3.78 mg Dibasic Sodium Phosphate I.P. as buffering agent, 16 mg Glycerol I.P. as tonicity modifier, 0.80 mg Liquified Phenol I.P as preservative/stabilizer, 1.76 mg Metacresol Ph. Eur. as preservative/stabilizer, 0.28 mg Protamine Sulfate I.P. as Insulin lispro complexing agent, Zinc Oxide I.P. q.s. as stabilizer, Hydrochloric Acid I.P. (10 %) q.s. and Sodium Hydroxide I.P. (10 %) q.s. for pH adjustment, Water for Injection I.P. q.s. 1mL.

Each mL of 50 % Insulin lispro and 50 % Insulin lispro Protamine Suspension contains: 100 IU (equivalent to 3.5 mg) Insulin Lispro I.P. (r-DNA origin) as active ingredient, 3.78 mg Dibasic Sodium Phosphate I.P. as buffering agent, 16 mg Glycerol I.P. as tonicity modifier, 1 mg Liquified Phenol I.P. as preservative/stabilizer, 2.20 mg Metacresol Ph. Eur. as preservative/stabilizer, 0.19 mg Protamine Sulfate I.P. as Insulin lispro complexing agent, Zinc Oxide I.P. q.s. as stabilizer, Hydrochloric Acid I.P. (10 %) q.s. and Sodium Hydroxide I.P. (10 %) q.s. for pH adjustment, Water for Injection I.P. q.s. 1mL

Insulin Lispro is synthesized in a special non-disease producing laboratory strain of Escherichia coli bacteria that has been genetically altered by the addition of the gene for Insulin lispro production.

PHARMACEUTICAL FORM

Suspension for injection.

Humalog Mix25® (25% insulin lispro and 75% insulin lispro protamine suspension) is available as a white sterile suspension for parenteral administration in a concentration of 100 IU/mL in 3 mL pre-filled insulin delivery devices.
Humalog® Mix50™ (50% insulin lispro and 50% insulin lispro protamine suspension) is available as a white sterile suspension for parenteral administration in a concentration of 100 IU/mL in 3 mL pre-filled insulin delivery devices.

CLINICAL PARTICULARS

Therapeutic indications

Humalog Mix25® and Humalog® Mix50™ are indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

Posology and method of administration

The dosage of Humalog Mix25® and Humalog® Mix50™ should be determined by the physician, according to the requirement of the patient.

Humalog Mix25® and Humalog® Mix50™ may be given shortly before meals. When necessary, Humalog Mix25® and Humalog® Mix50™ can be given soon after meals. Humalog Mix25® and Humalog® Mix50™ should only be given by subcutaneous injection. Under no circumstances should Humalog Mix25® and Humalog® Mix50™ be given intravenously.

Subcutaneous administration should be in the upper arms, thighs, buttocks, or abdomen. Use of injection sites should be rotated so that the same site is not used more than approximately once a month.

When administered subcutaneously 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. Patients must be educated to use the proper injection techniques.

The rapid onset and early peak of activity of Humalog® itself is observed following the subcutaneous administration of Humalog Mix25® and Humalog® Mix50™. This allows Humalog Mix25® and Humalog® Mix50™ to be given very close to mealtime. The duration of action of the insulin lispro protamine suspension (BASAL) component of Humalog Mix25® and Humalog® Mix50™ is similar to that of a basal insulin NPH.
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 Mix25® and Humalog® Mix50™ is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Contraindications

Hypersensitivity to insulin lispro or to any of the excipients.

Hypoglycemia.

Special warnings and precautions for use

Under no circumstances should Humalog Mix25® and Humalog® Mix50™ be given intravenously.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. 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.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease or medications such as beta-blockers.

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. Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

The use of dosages which are inadequate or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Insulin requirements may be reduced in the presence of renal impairment.
Insulin requirements may be reduced in patients with hepatic impairment due to reduced capacity for gluconeogenesis and reduced insulin breakdown; however, in patients with chronic hepatic impairment, an increase in insulin resistance may lead to increased insulin requirements.

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. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

Combination of Humalog with pioglitazone: Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind, if treatment with the combination of pioglitazone and Humalog is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued, if any deterioration in cardiac symptoms occurs.

Administration of insulin lispro to children below 12 years of age should be considered only in case of an expected benefit when compared to regular insulin.

Instructions for use and handling
To prevent the possible transmission of disease, each pen must be used by one patient only, even if the needle is changed.

Interaction with other medicinal products and other forms of interaction

Insulin requirements may be increased by substances with hyperglycaemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy, danazol, beta$_2$ stimulants (such as ritodrine, salbutamol, terbutaline).

Insulin requirements may be reduced in the presence of medicinal products with hypoglycaemic activity, such as oral hypoglycemics, salicylates (for example, acetylsalicylic acid), sulpha antibiotics, certain antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors), certain angiotensin converting enzyme inhibitors (captopril, enalapril), angiotensin II receptor blockers, beta-blockers, octreotide or alcohol.

Mixing Humalog Mix25® or Humalog® Mix50™ with other insulins has not been studied.

The physician should be consulted when using other medications in addition to Humalog Mix25® and Humalog® Mix50™ (see also section *Special warnings and precautions for use*).

Fertility, pregnancy and lactation

Data on a large number of exposed pregnancies do not indicate any adverse effect of insulin lispro on pregnancy or on the health of the foetus/newborn.
It is essential to maintain good control of the insulin-treated (insulin-dependent or gestational diabetes) patient 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 glucose control, as well as general health, is essential in pregnant patients with diabetes.
Patients with diabetes who are breast-feeding may require adjustments in insulin dose, diet or both.

Effects on ability to drive and use machines

The patient's ability to concentrate and 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 whilst 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.

Undesirable effects

Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia is a result of both the insulin dose and other factors e.g. a patient's level of diet and exercise.

Local allergy in patients is common (1/100 to <1/10). Redness, swelling, and itching can occur 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, which is rare (1/10,000 to <1/1,000) but potentially more serious, is a generalised allergy to insulin. It may cause a 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 at the injection site is uncommon (1/1,000 to <1/100).

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

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 activity 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.

Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmaco-therapeutic group: ATC Code: A10A D04.

Humalog Mix25® and Humalog® Mix50™ are premixed suspension consisting of insulin lispro (fast-acting human insulin analogue) and insulin lispro protamine suspension (intermediate acting human insulin analogue).

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PPD Information Box

Start Date 05 JUL 2018	**Proof No. :** 1	**Printing Colours** BLACK	**Technical Colours** Die Cut
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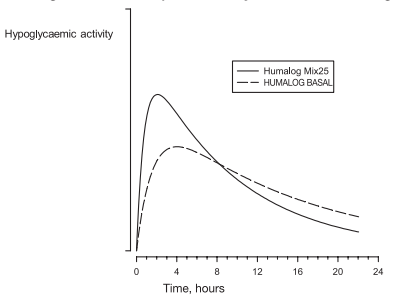
The primary activity of insulin lispro is the regulation of glucose metabolism.

In addition, insulins have several anabolic and anti-catabolic actions on a variety of different tissues. Within muscle tissue this includes increasing glycogen, fatty acid, glycerol and protein synthesis and amino acid uptake, while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

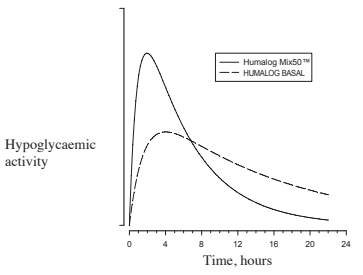
Insulin lispro has a rapid onset of action (approximately 15 minutes), thus allowing it to be given closer to a meal (within zero to 15 minutes of the meal) when compared to regular insulin (30 to 45 minutes before). The rapid onset and early peak of activity of insulin lispro is observed following the subcutaneous administration of Humalog Mix25® and Humalog® Mix50™. HUMALOG BASAL has an activity profile that is very similar to that of a basal insulin (NPH) over a period of approximately 15 hours.

Clinical trials in patients with type 1 and type 2 diabetes have demonstrated reduced postprandial hyperglycaemia with Humalog Mix25® compared to human insulin mixture 30/70. In one clinical study there was a small (0.38 mmol/l) increase in blood glucose levels at night (3a.m.).

In the figure below the pharmacodynamics of Humalog Mix25® and HUMALOG BASAL are illustrated.



In the figure below the pharmacodynamics of Humalog® Mix50™ and HUMALOG BASAL are illustrated.



The above representation reflects the relative amount of glucose over time required to maintain the subject's whole blood glucose concentrations near fasting levels and is an indicator of the effect of these insulins on glucose metabolism over time.

The glucodynamic response to insulin lispro is not affected by renal or hepatic function impairment. Glucodynamic differences between insulin lispro and soluble human insulin, as measured during a glucose clamp procedure, were maintained over a wide range of renal function.

Insulin lispro has been shown to be equipotent to human insulin on a molar basis but its effect is more rapid and of a shorter duration.

In two 8-month open label crossover studies, type 2 diabetes patients who were either new to insulin therapy or already using one or two injections of insulin, received 4 months of treatment with Humalog Mix25® (used twice daily with metformin) and insulin glargine (used once daily with metformin) in a randomised sequence. Detailed information can be found in the following table.

	Insulin-Naive Patients n = 78	**Not Insulin-Naive Patients** n = 97
Mean total daily insulin dose at endpoint	0.63 U/kg	0.42 U/kg
Haemoglobin A1c –Reduction[1]	1.30% (mean at baseline = 8.7%)	1.00 % (mean at baseline = 8.5%)
Reduction of the mean of combined morning / evening two-hour postprandial blood glucose[1]	3.46 mM	2.48 mM
Reduction of the mean fasting blood glucose[1]	0.55 mM	0.65 mM
Incidence of hypoglycaemia at endpoint	25%	25%
Bodyweight gain[2]	2.33 kg	0.96 kg

[1] from baseline to end of Humalog Mix25® treatment
[2] in patients randomised to Humalog Mix25® during the first crossover period

Pharmacokinetic properties

The pharmacokinetics of insulin lispro reflect a compound that is rapidly absorbed, and achieves peak blood levels 30 to 70 minutes following subcutaneous injection. The pharmacokinetics of insulin lispro protamine suspension are consistent with those of an intermediate acting insulin such as NPH. The pharmacokinetics of Humalog® Mix25 and Humalog® Mix50™ are representative of the individual pharmacokinetic properties of the two components. When considering the clinical relevance of these kinetics, it is more appropriate to examine the glucose utilisation curves (as discussed in section *Pharmacodynamic properties*).

Insulin lispro maintains more rapid absorption when compared to soluble human insulin in patients with renal impairment. In patients with type 2 diabetes over a wide range of renal function the pharmacokinetic differences between insulin lispro and soluble human insulin were generally maintained and shown to be independent of renal function. Insulin lispro maintains more rapid absorption and elimination when compared to soluble human insulin in patients with hepatic impairment.

Preclinical safety data

In *in vitro* tests, including binding to insulin receptor sites and effects on growing cells, insulin lispro behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin lispro is equivalent to human insulin. Acute, one month and twelve month toxicology studies produced no significant toxicity findings.

Insulin lispro did not induce fertility impairment, embryotoxicity or teratogenicity in animal studies.

PHARMACEUTICAL PARTICULARS

List of excipients:

Dibasic Sodium Phosphate
Glycerol
Liquified Phenol
Metacresol
Protamine Sulfate
Zinc Oxide
Hydrochloric Acid
Sodium Hydroxide
Water for Injection

Incompatibilities

Mixing Humalog Mix25® and Humalog® Mix50™ with other insulins has not been studied. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf Life

Unused pre-filled pens
3 years.

After first use
28 days.

Special precautions for storage

Unused pre-filled pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not expose to excessive heat or direct sunlight.

After first use
Store below 30°C. Do not refrigerate. The pre-filled pen should not be stored with the needle attached.

Nature and contents of container

The suspension is contained in type I flint glass cartridges, sealed with butyl or halobutyl disc seals and plunger heads and secured with aluminium seals. Dimeticone or silicone emulsion may have been used to treat the cartridge plunger, and/or the glass cartridge. The 3 mL cartridges are sealed in a disposable pen injector, called the "KwikPen™". Needles are not included.

Humalog Mix25® KwikPen™ is available in pack of 5 x 3 mL Pens.
Humalog® Mix50™ KwikPen™ is available in pack of 5 x 3 mL Pens.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling
To prevent the possible transmission of disease, each pen must be used by one patient only, even if the needle is changed.

Instructions for use, handling and disposal

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

1. Be sure to check your insulin for:
   - Type
   - Expiration date
   - Appearance
2. Wash your hands.
3. Choose a site for injection.
4. Clean the skin as instructed.

a) Preparing a dose :

1. Inspect the Humalog Mix25® KwikPen™ and Humalog® Mix50™ KwikPen™ 100 IU/mL Pen.
The Pen should be rotated in the palms of the hands ten times and inverted 180° ten times immediately before use to resuspend the insulin until it appears uniformly cloudy or milky. If not, repeat the above procedure until contents are mixed. Cartridges contain a small glass bead to assist mixing. Do not shake vigorously as this may cause frothing which may interfere with the correct measurement of the dose. The cartridges should be examined frequently and should not be used if clumps of material are present or if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance.
2. Remove paper tab from Outer Needle Shield. Wipe the rubber seal with alcohol. Remove the paper tab from the capped needle. Screw the capped needle clockwise onto the pen until it is tight. Hold the pen with needle pointing up and remove the outer needle cap and inner needle cover.
3. Priming Pen (check insulin flow).
(a) Pull off Outer Needle Shield. **Do not** throw away. Pull off Inner Needle Shield and throw away.
(b) Turn dose knob clockwise until a "2" appears in the dose window.
(c) Hold the pen with needle pointing up and tap the cartridge holder gently with your finger so any air bubbles collect near the top. With needle pointed up, push Dose Knob in until it stops and 0 is seen in the Dose Window. Hold Dose Knob in and **count slowly for 5 seconds**. Priming is complete when a stream of insulin appears from the needle tip. If a stream of insulin does not appear, repeat priming steps. If you do not see a stream of insulin from the needle tip and dialing the Pen is more difficult, change the needle and prime the Pen.
(d) Always prime the pen (check the insulin flow) before each injection. Failure to prime the pen may result in an inaccurate dose.

b) Injecting a dose :

1. Turn Dose Knob to the number of units you need to inject. If you dial too many units, you can correct the dose by dialing backwards. The odd numbers are shown as full lines between the even numbers.
2. Stabilise the skin by spreading it or pinching up a large area. Insert the needle using injection technique recommended by your healthcare professional.
3. Place your thumb on the Dose Knob and push firmly until the Dose Knob stops moving. To deliver the full dose, hold Dose Knob in and **count slowly for 5 seconds**. Remove needle from skin.
Press the injection button down with the thumb (until you hear or feel a click); wait 5 seconds.
4. Pull the needle out and apply gentle pressure over the injection site for several seconds. Do not rub the area. Check to make sure you see 0 in the Dose Window to confirm you received the complete dose.
5. Immediately after an injection, use the outer needle cap to unscrew the needle. Remove the needle from the pen. This will ensure sterility, and prevent leakage, re-entry of air, and potential needle clogs. Do not reuse the needle. Dispose of the needle in a responsible manner. Needles and pens must not be shared. The pre-filled pen can be used until it is empty. Please properly discard or recycle.
6. Replace the cap on the pen.
7. Use of injection sites should be rotated so that the same site is not used more than approximately once a month.
8. The injection button should be fully depressed before using the pen again.

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If you have any questions or complaints with your Humalog KwikPen®, contact Lilly at Toll Free number 18001230021 or your healthcare professional for assistance

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For more information, visit us at www.lillyindia.co.in

PA002ITIN01

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