Special precautions for storage

Store at 2°C - 8°C (in a refrigerator).
Do not freeze.
Do not expose to excessive heat or direct sunlight.
Once in use cartridges may be used for up to 28 days. Following insertion in a pen, the cartridge and pen should be stored below 30°C and should not be refrigerated.
The pen with the inserted cartridge 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.

5 x 3 mL Humalog Mix25® and Humalog® Mix50 cartridges for a 3 mL pen.

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 cartridge must be used by one patient only, even if the needle on the delivery device is changed.

Instructions for use, handling and disposal

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

a) Preparing a dose
Cartridges containing Humalog Mix25® and Humalog® Mix50 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.

Humalog Mix25® and Humalog® Mix50 cartridges are not designed to allow any other insulin to be mixed in the cartridge. Cartridges are not designed to be refilled.

The following is a general description. The manufacturer's instructions with each individual pen must be followed for loading the cartridge, attaching the needle and administering the insulin injection.

b) Injecting a dose
1. Wash your hands.
2. Choose a site for injection.
3. Clean the skin as instructed.
4. Remove outer needle cap.
5. Stabilise the skin by spreading it or pinching up a large area. Insert the needle as instructed.
6. Press the knob.
7. Pull the needle out and apply gentle pressure over the injection site for several seconds. Do not rub the area.
8. Using the outer needle cap, unscrew the needle and dispose of it safely.
9. Use of injection sites should be rotated so that the same site is not used more than approximately once a month.

Manufactured by :
LILLY FRANCE S.A.S.
Centre de Production,
2, Rue Du Colonel Lilly,
Zone Industrielle,
F-67640 Fegersheim,
France

***Marketed By:**
Eli Lilly and Company (India) Pvt. Ltd.
Plot No. 92, Sector-32, Gurgaon-122001, Haryana, India

Imported By:
Eli Lilly and Company (India) Pvt. Ltd., Bldg. No. 14, Gala No. 1 to 4, 1st Fl, Arihant Comm. Complex, Purna Bhiwandi, Maharashtra-421302

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

* Under licence from registered trademark owners
Eli Lilly and Company, USA

Humalog® cartridges are designed to be used only with Lilly insulin delivery devices.

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

PA691FSRI07

VL7393/VL7394 **For more information, visit us at www.lillyindia.co.in**

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

Humalog Mix25®

(100 IU/mL, 3 mL Cartridge)
[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

(100 IU/mL, 3 mL Cartridge)
[Monocomponent Insulin lispro, recombinant DNA origin]

Lilly

NAME OF THE MEDICINAL PRODUCT

Humalog Mix25® 100 IU/mL suspension for injection in cartridge
Humalog® Mix50 100 IU/mL suspension for injection in cartridge

QUALITATIVE AND QUANTITATIVE COMPOSITION

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 USP 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 USP 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® is a white, sterile suspension.
Suspension for injection. Humalog® Mix50 is a white, sterile suspension.

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 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 Insulin Lispro itself is observed following the subcutaneous administration of Humalog Mix25® and Humalog® Mix50. This allows Humalog Mix25® 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

Humalog Mix25® and Humalog® Mix50 are contraindicated during episodes of hypoglycemia.
Humalog Mix25® and Humalog® Mix50 are contraindicated in patients with hypersensitivity to insulin lispro or any of the excipients contained in the formulation.

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 cartridge must be used by one patient only, even if the needle on the delivery device 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 substances with hypoglycaemic activity, such as oral hypoglycaemics, 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® and 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.

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*).

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.

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).

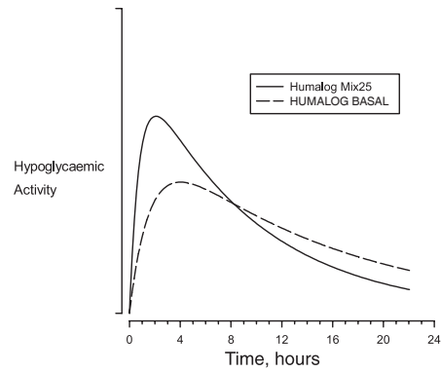
The primary activity of insulin lispro is the regulation of glucose metabolism.

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.

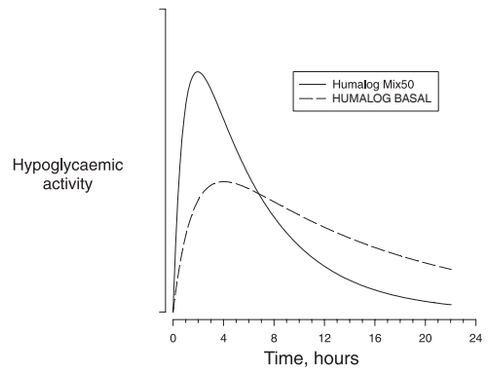
Insulin lispro has a rapid onset of action (approximately 15 minutes), thus allowing it to be given closer to a meal (within zero to 15 minutes of the meal) when compared to regular insulin (30 to 45 minutes before). The rapid onset and early peak of activity of insulin lispro is observed following the 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	**Not Insulin-Naive Patients**
	n = 78	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 *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

3 years

After insertion of the cartridge in a pen, the suspension should be used in 28 days when stored below 30°C.

PA691FSRI07

Item Code PA691FSRI07			**Previous Item Code** *(to be destroyed)* PA691FSRI06		
PPD Information Box				**ALRP Information Box**	
Start Date 05 JUN 2018	**Proof No. :** 1	**Printing Colours** BLACK	**Technical Colours** Die Cut	**Affiliate Barcode:** **Type:** N/A **Code:** N/A	**Translations of Variable Data**
Technical Information: **Layout name** FEGPA018A03	**Size (mm):** 300x315			**Other Regulated Elements** N/A	**lot:** N/A
	Folded Size (mm) 150x54				**mfg date:** N/A
	No. of Pages: 2/2				**exp date:** N/A
BLUE Project No. 1800029324	**Sick Code** N/A		**Overt** N/A		**price:** N/A
Feed Direction: (For labels only)	N/A ✔				**other:** N/A
Lilly Answers That Matter. v5.4				**Site:** Fegersheim	
SCHAWK!™ Riverside Drive, Cleckheaton, West Yorkshire, BD19 4DH, United Kingdom Tel: +44 (0) 127 484 8000 www.schawk.com			Internal to Schawk (no Lilly check required) Schawk Artwork Ref: 101043502_400984700 Operator Name: AL		