PA002ITPL01

Insulin Lispro

Humalog® Mix50 KwikPen

100 Units/mL Suspension for Injection

1. NAME OF THE MEDICINAL PRODUCT

Insulin Lispro (Humalog® Mix50 KwikPen) 100 units/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General

Insulin Lispro (Humalog® Mix50 KwikPen) is a white, sterile suspension.

2.2 Qualitative and quantitative composition

One mL contains 100 units (equivalent to 3.5 mg) insulin lispro Ph. Eur. (recombinant DNA origin produced in *E.coli*). Each container includes 3 mL equivalent to 300 units insulin lispro.

Insulin Lispro (Humalog® Mix50 KwikPen) consists of 50% insulin lispro solution and 50% insulin lispro protamine suspension.

For a full list of excipients, see section 7.1.

3. PHARMACOLOGIC CATEGORY

Antidiabetic

4. PHARMACEUTICAL FORM

Suspension for injection.

5. CLINICAL PARTICULARS

5.1 Therapeutic indications

Insulin Lispro (Humalog® Mix50 KwikPen) is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

5.2 Posology and method of administration

Posology

The dosage should be determined by the physician, according to the requirement of the patient.

Insulin Lispro (Humalog® Mix50 Kwikpen) may be given shortly before meals. When necessary, Insulin Lispro (Humalog® Mix50 Kwikpen) can be given soon after meals. Insulin Lispro (Humalog® Mix50 Kwikpen) should only be given by subcutaneous injection. Under no circumstances should Insulin Lispro (Humalog® Mix50 Kwikpen) be given intravenously.

The rapid onset and early peak of activity of Insulin lispro (Humalog®) itself is observed following the subcutaneous administration of Insulin lispro protamine (Humalog® Mix50 Kwikpen). This allows Insulin Lispro (Humalog® Mix50 to be given very close to mealtime. The duration of action of the insulin lispro protamine suspension component of Insulin Lispro (Humalog® Mix50 Kwikpen) 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 Insulin Lispro (Humalog® Mix50 KwikPen) is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Special populations

Renal impairment

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

Hepatic 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.

Pediatric population

Administration of Insulin Lispro (Humalog® Mix50 KwikPen) to children below 12 years of age should be considered only in case of an expected benefit when compared to soluble insulin.

Method of administration

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, in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

When administered subcutaneously care should be taken when injecting Insulin lispro (Humalog® Mix50 Kwikpen) 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 KwikPen delivers 1 – 60 units in steps of 1 unit in a single injection. The needed dose is dialed in units. **The number of units is shown in the dose window of the pen.**

5.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 7.1.

Hypoglycemia.

5.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Under no circumstances should Insulin lispro (Humalog® Mix50 KwikPen) be given intravenously.

Transferring a patient to another type or brand of insulin

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular/soluble, NPH/isophane, 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.

Hypoglycemia and hyperglycemia

Conditions which may make the early warning symptoms of hypoglycemia 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 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. Uncorrected hypoglycemic or hyperglycemic 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 hyperglycemia and diabetic ketoacidosis; conditions which are potentially lethal.

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.

Insulin requirements and dosage adjustment

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 hypoglycemia.

Combination of Insulin Lispro (Humalog® Mix50 KwikPen) 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 Insulin Lispro (Humalog® Mix50 KwikPen) is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and edema. Pioglitazone should be discontinued, if any deterioration in cardiac symptoms occurs.

Avoidance of medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups with other insulin products.

Patients must visually verify the dialed units on the dose counter of the pen. Therefore, the requirement for patients to self-inject is that they can read the dose counter on the pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially "sodium free".

5.5 Interaction with other medicinal products and other forms of interaction

Insulin requirements may be increased by substances with hyperglycemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy, danazol, beta2 stimulants (such as ritodrine, salbutamol, terbutaline).

Insulin requirements may be reduced in the presence of substances with hypoglycemic 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 Insulin Lispro (Humalog® Mix50 KwikPen) with other insulins has not been studied.

The physician should be consulted when using other medications in addition to Insulin Lispro (Humalog® Mix50 KwikPen). (see section 5.4)

5.6 Fertility, pregnancy and lactation

Pregnancy

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 fetus/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.

Breastfeeding

Patients with diabetes who are breast-feeding may require adjustments in insulin dose, diet or both.

Fertility

Insulin lispro did not induce fertility impairment in animal studies (see section 6.3).

5.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. 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 hypoglycemia whilst driving, this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

5.8 Undesirable effects

Summary of safety profile

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

Tabulated list of adverse reactions

The following related adverse reactions from clinical trials are listed below as MedDRA preferred term by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000) ; not known (cannot be estimated form the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders						
Local allergy		X				
Systemic allergy				X		
Skin and subcutaneous tissue disorders						
Lipodystrophy			X			
Cutaneous amyloidosis						X

BLUE 50235

Reviewed by: Renaida Espedido
Date: 01.09.2023

Verified by: Czarina Mateo
Date: 01.11.2023

PPD Information Box

Technical Information: ■ BLACK ☐ DIECUT

Previous Item Code
(to be destroyed)
PA002ITPL00

Lilly

Description of selected adverse reactions

Local allergy

Local allergy in patients is common. 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

Systemic allergy, which is rare but potentially more serious, is a generalized 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 generalized allergy may be life-threatening.

Skin and subcutaneous tissue disorders

Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

Edema

Cases of edema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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. Refer to section 12.

5.9 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. Hypoglycemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

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

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

Correction of moderately severe hypoglycemia 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 hypoglycemia may recur after apparent clinical recovery.

6. PHARMACOLOGICAL PROPERTIES

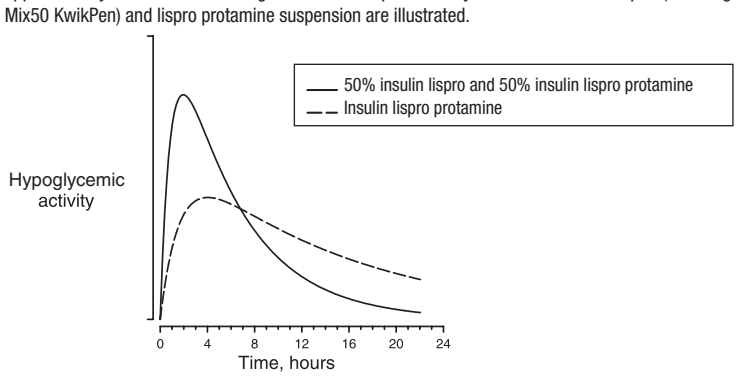
6.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate or long acting combined with fast acting. ATC Code: A10A D04

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 soluble insulin (30 to 45 minutes before). The rapid onset and early peak of activity of insulin lispro is observed following the subcutaneous administration of Insulin Lispro (Humalog® Mix50 KwikPen). Insulin lispro protamine suspension has an activity profile that is very similar to that of a basal insulin over a period of approximately 15 hours. In the figure below the pharmacodynamics of Insulin Lispro (Humalog® Mix50 KwikPen) and lispro protamine suspension 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 effects 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.

6.2 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 Insulin Lispro (Humalog® Mix50 Kwikpen) 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 utilization curves (as discussed in 6.1).

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.

6.3 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.

7. PHARMACEUTICAL PARTICULARS

7.1. List of excipients

Protamine sulphate
m-cresol [2.20 mg/mL] as preservative
Phenol [0.89 mg/mL] as preservative
Glycerol
Dibasic sodium phosphate $7H_2O$
Zinc oxide
Water for injections
Hydrochloric acid and sodium hydroxide may be used to adjust pH to 7.0 - 7.8.

7.2. Incompatibilities

Mixing 50% Insulin lispro and 50% Insulin lispro protamine (Humalog® Mix50 KwikPen) with other insulins has not been studied. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

7.3. Shelf life

Before use

3 years.

After first use

28 days.

7.4. Special precautions for storage

Do not freeze. Do not expose to excessive heat or direct sunlight.

Before use

Store in a refrigerator (2°C - 8°C).

After first use

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

7.5. Nature and contents of container

The suspension is contained in type I flint glass cartridges, sealed with halobutyl disc seals and plunger heads and are secured with aluminum seals. Dimeticone or silicone emulsion may have been used to treat the cartridge plunger, and/or the glass cartridge

7.6. Special precautions for disposal and other handling

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. The patient should discard the needle after every injection.

The Insulin Lispro (Humalog® Mix50 KwikPen) 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.

Preparing a dose

The KwikPen containing Insulin Lispro (Humalog® Mix50 KwikPen) 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 dose.

Before using the KwikPen the user manual included in the package leaflet must be read carefully. The KwikPen has to be used as recommended in the user manual.

Pens should not be used if any part looks broken or damaged.

Injecting a dose

If using a pre-filled pen refer to the detailed instructions for preparing the pen and injecting the dose, the following is a general description.

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

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

8. AVAILABILITY

3 mL Pre-filled Pen (Box of 5s)

9. IMPORTED AND DISTRIBUTED BY

Zuellig Pharma Corporation
Km. 14 West Service Rd., South Superhighway corner Edison Ave.
Sun Valley, Parañaque City, Philippines

10. MANUFACTURED BY

Eli Lilly Italia S.p.A.
V. Gramsci, 731-733-50019
Sesto Fiorentino (Firenze), Italy

11. CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

12. ADR Reporting Statement

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

13. REGISTRATION NUMBER

BR-990

14. DATE OF FIRST AUTHORIZATION

31 October 2014

15. DATE OF REVISION OF THE PACKAGE INSERT

December 2022

EU SPC 03Sep2020

PA002ITPL01