PA000FSIN01

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Insulin Lispro I.P. (rDNA Origin),

Solution for Injection in Pre-Filled Pen 200 U/mL

Humalog® 200U/mL KwikPen™

1. NAME OF THE MEDICINAL PRODUCT

Humalog® 200U/mL Kwikpen™, solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Insulin Lispro contains: 200 IU (equivalent to 6.9 mg) Insulin lispro I.P. (r-DNA origin) as active ingredient, 16 mg Glycerol I.P. as Tonicity Modifier, 3.15 mg Metacresol Ph.Eur. as preservative/stabilizer, Zinc Oxide I.P. q.s. as stabilizer, 5 mg Trometamol Ph. Eur. as Buffering agent, Hydrochloric Acid 10% I.P. q.s. and Sodium Hydroxide 10% I.P. q.s. for pH adjustment, Water for Injection I.P. q.s. 1mL.

3. PHARMACEUTICAL FORM

Solution for injection. KwikPen.
Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of adults with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog® 200U/mL Kwikpen™ is also indicated for the initial stabilisation of diabetes mellitus.

4.2 Posology and method of administration

Posology

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

Humalog may be given shortly before meals. When necessary Humalog can be given soon after meals.

Humalog takes effect rapidly and has a shorter duration of activity (2 to 5 hours) given subcutaneously as compared with regular insulin. This rapid onset of activity allows a Humalog injection to be given very close to mealtime. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. The faster onset of action compared to soluble human insulin is maintained regardless of injection site. The duration of action of Humalog is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Humalog can be used in conjunction with a longer-acting insulin or oral sulphonylurea medicinal products, on the advice of a physician.

Humalog 100 units/ml Kwikpen® and Humalog® 200U/mL Kwikpen™

Humalog KwikPen is available in two strengths. For both, the needed dose is dialled in units. Both pre-filled pens, the Humalog 100 units/ml Kwikpen® and the Humalog 200 units/ml KwikPen deliver
1-60 units in steps of 1 unit in a single injection. The number of units is shown in the dose window of the pen regardless of strength and **no** dose conversion should be done when transferring a patient to a new strength.
Humalog® 200U/mL Kwikpen™ should be reserved for the treatment of patients with diabetes requiring daily doses of more than 20 units of rapid-acting insulin. The insulin lispro solution containing 200 units/ml should not be withdrawn from the pre-filled pen (the KwikPen) or mixed with any other insulin (see section 4.4 Special warnings and precautions for use and section 6.2 Incompatibilities)

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.

Method of administration
Humalog solution for injection should be given subcutaneously.

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 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.

Humalog® 200U/mL Kwikpen™ solution for injection should not be used in an insulin infusion pump.

Humalog® 200U/mL Kwikpen™ solution for injection should not be used intravenously.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypoglycaemia.

4.4 Special warnings and precautions for use

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, 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. For fast-acting insulins, any patient also on basal insulin must optimise dosage of both insulins to obtain glucose control across the whole day, particularly nocturnal/fasting glucose control.

Hypoglyceamia and hyperglyceamia
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 medicinal products 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 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 hypoglycaemia. A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

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.

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.

Avoidance of medication errors when using insulin lispro (200 units/ml) in pre-filled pen:
The insulin lispro solution for injection containing 200 units/ml must not be transferred from the pre-filled pen, the KwikPen, to a syringe. The markings on the insulin syringe will not measure the dose correctly. Overdose can result causing severe hypoglycemia. The insulin lispro solution for injection containing 200 units/ml must not be transferred from the KwikPen to any other insulin delivery device, including insulin infusion pumps.
Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Humalog as well as other insulin products.

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

4.5 Interaction with other medicinal products and other forms of interaction

Insulin requirements may be increased by medicinal products 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.

The physician should be consulted when using other medicinal products in addition to Humalog® 200U/mL Kwikpen™ (see section 4.4 Special warnings and precautions for use).

4.6 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 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.

Breast-feeding
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 5.3 Preclinical safety data)

4.7 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 using machines).

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.

4.8 Undesirable effects

Summary of safety profile

Hypoglycaemia is the most frequent adverse reaction of insulin lispro 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.

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).

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

MedDRA system organ classes	Very common	Common	Uncommon	Rare	Very rare
Immune system disorders					
Local allergy		X			
Systemic allergy				X	
Skin and subcutaneous tissue disorders					
Lipodystrophy			X		

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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 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
Lipodystrophy at the injection site is uncommon.

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

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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

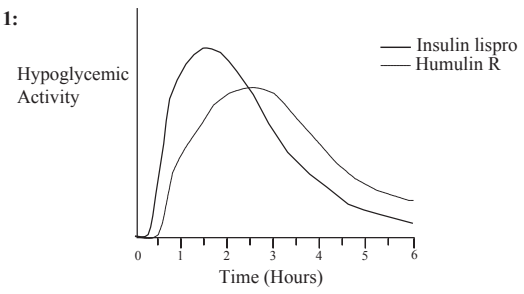
The primary activity of insulin lispro is the regulation of glucose metabolism.

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). Insulin lispro takes effect rapidly and has a shorter duration of activity (2 to 5 hours) when compared to regular insulin.

Clinical trials in patients with type 1 and type 2 diabetes have demonstrated reduced postprandial hyperglycaemia with insulin lispro compared to soluble human insulin.
The time course of insulin lispro action may vary in different individuals or at different times in the same individual and is dependent on dose, site of injection, blood supply, temperature and physical activity. The typical activity profile following subcutaneous injection is illustrated below.

Figure 1:



The above representation (figure 1) 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 (100 units/ml) on glucose metabolism over time.

The pharmacodynamic responses of insulin lispro 200 units/ml solution for injection were similar to those for insulin lispro 100 units/ml solution for injection after subcutaneous administration of a single 20 unit dose in healthy subjects as shown in the graph below (figure 2).

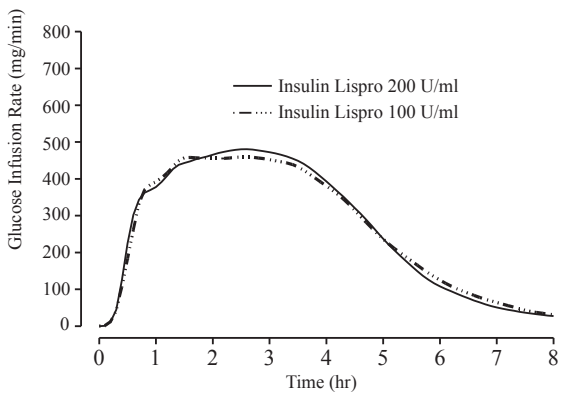


Figure 2: Arithmetic mean glucose infusion rate versus time profiles following subcutaneous administration of 20 units of insulin lispro 200 units/ml or insulin lispro 100 units/ml

In patients with type 2 diabetes on maximum doses of sulphonyl urea agents, studies have shown that the addition of insulin lispro significantly reduces HbA1c compared to sulphonyl urea alone. The reduction of HbA1c would also be expected with other insulin products e.g. soluble or isophane insulins.

Clinical trials in patients with type 1 and type 2 diabetes have demonstrated a reduced number of episodes of nocturnal hypoglycaemia with insulin lispro compared to soluble human insulin. In some studies, reduction of nocturnal hypoglycaemia was associated with increased episodes of daytime hypoglycaemia.

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.

5.2 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. When considering the clinical relevance of these kinetics, it is more appropriate to examine the glucose utilisation curves (as discussed in 5.1).

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.

Insulin lispro 200 units/ml solution for injection was bioequivalent to insulin lispro 100 units/ml solution for injection after subcutaneous administration of a single 20 unit dose in healthy subjects. Time to maximum concentration was also similar between formulations.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Glycerol
Trometamol
Zinc oxide
Water for injections
Hydrochloric acid and sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

This medicinal product should not be mixed with any other insulin or any other medicinal product. The solution for injection should not be diluted.

6.3 Shelf life

Unused pre-filled pens
3 years.

After first use
28 days.

6.4 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.

6.5 Nature and contents of container

Type I glass cartridges, sealed with chlorobutyldisc seals and plunger heads and secured with aluminium seals. Dimeticone or silicone emulsion may be used to treat the cartridge plunger, and/or the glass cartridge. The 3 ml cartridges which contain 600 units insulin lispro (200 units/ml), are sealed in a disposable pen injector, called the "KwikPen". Needles are not included.

6.6 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 Humalog solution should be clear and colourless. Humalog should not be used if it appears cloudy, thickened, or slightly coloured or if solid particles are visible.

Handling of the pre-filled pen
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.

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

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If you have any questions or complaints with your Humalog® 200U/mL KwikPen™, contact Lilly at Toll Free number 18001230021 or your healthcare professional for assistance

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