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## Insulin Lispro Injection

### DRUG NAME

Generic name: Insulin Lispro Injection

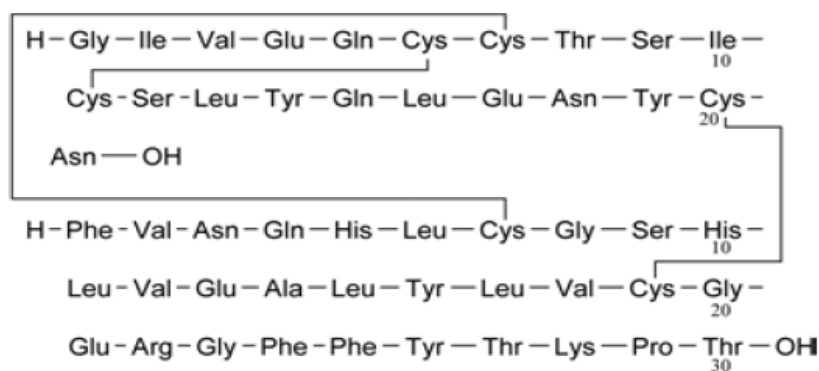
Trade name: Prandilin™

### COMPOSITION

Active ingredient: Insulin Lispro

Chemical name: 28<sup>B</sup>-L-Lysine-29<sup>B</sup>-L-proline insulin

Chemical structural formula:



Molecular formula:  $C_{257}H_{383}N_{65}O_{77}S_6$

Molecular weight: 5808 Da

Excipient: Zinc oxide, M-cresol, Glycerol, Sodium phosphate dibasic anhydrous, Hydrochloric acid (for pH adjustment), Sodium hydroxide (for pH adjustment), Water for injections

### DESCRIPTION

Clear, colorless, sterile solution filled in colorless and transparent cartridge

### INDICATION

Prandilin is a rapid acting human insulin analogue indicated to improve glycemic control in adults with diabetes mellitus.

### STRENGTHS

100 units/mL in 3-mL cartridge

### DOSAGE AND ADMINISTRATION

Usage:

Prandilin takes effect rapidly and should be administered subcutaneously shortly before meals (within 15 minutes before a meal). Care should be taken when injecting Prandilin to ensure that a blood vessel has not been damaged.

Injection sites must be rotated within a given injection area from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis.

Wipe the skin with an alcohol swab to clean the injection site. Let the injection site dry before you inject your dose.

Please bring Prandilin to room temperature before use and follow the injection steps described below:

- (1) Check the insulin to make sure it is clear and colorless. Do not use Prandilin if it is colored or cloudy, or if you see particles in the solution.
- (2) Please refer to the relevant reusable pen package insert, when using Prandilin in conjunction with a reusable pen.
- (3) Prandilin is injected under the skin (subcutaneously) of the upper arm, thigh, or stomach area (abdomen). Wipe the skin with an alcohol swab to clean the injection site. Let the injection site dry before injection. Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localised cutaneous amyloidosis.
- (4) Pinch the skin of the injection site with your fingers and puncture the needle. After the pusher is pushed to the end, keep the needle under the skin for a few seconds to ensure that the correct dose is injected, then pull out the needle, and gently press the injection site with the sterile cotton ball for a few seconds, but do not rub the injection site to avoid damage to the subcutaneous tissue or cause the exudation of Prandilin.

**Dosage:**

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

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

Prandilin takes effect rapidly and has a shorter duration of activity (2 to 5 hours) given subcutaneously as compared with soluble insulin. This rapid onset of activity allows a Prandilin 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. As with all insulin preparations, the duration of action of Prandilin is dependent on dose, site of injection, blood supply, temperature, and physical activity.

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

### *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.

#### *Paediatric population*

Prandilin can be used in adolescents and children.

## **ADVERSE REACTIONS**

### **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:  $\geq 1/10$ ; common:  $\geq 1/100$  to  $< 1/10$ ; uncommon:  $\geq 1/1,000$  to  $< 1/100$ ; rare:  $\geq 1/10,000$  to  $< 1/1,000$ ; very rare:  $< 1/10,000$ ).

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

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

### **Hypoglycemia:**

Hypoglycemia is the most common adverse reaction associated with insulins, including Prandilin. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) or in patients who experience recurrent hypoglycemia.

### **Hypokalemia:**

All insulin products, including Prandilin, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for

hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

#### **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 cases it may be necessary to discontinue this product. 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.

#### **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.

#### **Oedema:**

Insulin may cause sodium retention and oedema particularly if previously poor metabolic control is improved by intensified insulin therapy.

#### **Clinical Trial Experience**

According to the literature, because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared with those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of Treatment-Emergent Adverse Events during Insulin Lispro clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

**Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (adverse events with frequency  $\geq 5\%$ )**

<b>Events, n (%)</b>	<b>Lispro (n=81)</b>	<b>Regular human insulin (n=86)</b>
Flu syndrome	28 (34.6)	28 (32.6)
Pharyngitis	27 (33.3)	29 (33.7)
Rhinitis	20 (24.7)	25 (29.1)
Headache	24 (29.6)	19 (22.1)
Pain	16 (19.8)	14 (16.3)
Cough increased	14 (17.3)	15 (17.4)
Infection	11 (13.6)	18 (20.9)
Nausea	5 (6.2)	13 (15.1)
Accidental injury	7 (8.6)	10 (11.6)

Events, n (%)	Lispro (n=81)	Regular human insulin (n=86)
Surgical procedure	5 (6.2)	12 (14.0)
Fever	5 (6.2)	10 (11.6)
Abdominal pain	6 (7.4)	7 (8.1)
Asthenia	6 (7.4)	7 (8.1)
Bronchitis	6 (7.4)	6 (7.0)
Diarrhea	7 (8.6)	5 (5.8)
Dysmenorrhea	5 (6.2)	6 (7.0)
Myalgia	6 (7.4)	5 (5.8)
Urinary tract infection	5 (6.2)	4 (4.7)

**Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (adverse events with frequency  $\geq 5\%$ )**

Events, n (%)	Lispro (n=714)	Regular human insulin (n=709)
Headache	83 (11.6)	66 (9.3)
Pain	77 (10.8)	71 (10.0)
Infection	72 (10.1)	54 (7.6)
Pharyngitis	47 (6.6)	58 (8.2)
Rhinitis	58 (8.1)	47 (6.6)
Flu syndrome	44 (6.2)	58 (8.2)
Surgical procedure	53 (7.4)	48 (6.8)

### Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII)

According to the literature, in a 12-week, randomized, crossover study in adult patients with type 1 diabetes (n=39), the rates of catheter occlusions and infusion site reactions were similar for Insulin Lispro and regular human insulin treated patients.

**Table 3: Catheter Occlusions and Infusion Site Reactions**

	Lispro (n=38)	Regular human insulin (n=39)
Catheter occlusions/month	0.09	0.10
Infusion site reactions	2.6% (1/38)	2.6% (1/39)

In a randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions were similar for insulin lispro and insulin aspart (21% of 100 patients versus 17% of 198 patients, respectively). In both groups, the most frequently reported infusion site adverse events were infusion site erythema and infusion site reaction.

### **Insulin initiation and intensification of glucose control**

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

### **Antibody Production**

According to the literature, in large clinical trials with patients with type 1 (n=509) and type 2 (n=262) diabetes mellitus, anti-insulin antibody (insulin lispro-specific antibodies, insulin-specific antibodies, cross-reactive antibodies) formation was evaluated in patients receiving both regular human insulin and Insulin Lispro (including patients previously treated with human insulin and naive patients). As expected, the largest increase in the antibody levels occurred in patients new to insulin therapy. The antibody levels peaked by 12 months and declined over the remaining years of the study. These antibodies do not appear to cause deterioration in glycemic control or necessitate an increase in insulin dose. There was no statistically significant relationship between the change in the total daily insulin dose and the change in percent antibody binding for any of the antibody types.

### **CONTRAINDICATIONS**

Prandilin is contraindicated to patients with hypersensitivity to the insulin lispro or to any of the excipients listed in **COMPOSITION**.

Prandilin is contraindicated to patients with hypoglycaemia.

### **PRECAUTIONS**

#### **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. 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/postprandial glucose control.

#### **Hypoglycaemia and hyperglycaemia**

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 and dosage adjustment**

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. 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 insulin lispro with pioglitazone**

Cases of cardiac failure have been reported when thiazolidinediones (e.g. 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 thiazolidinediones and Prandilin is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Thiazolidinediones should be discontinued, if any deterioration in cardiac symptoms occurs.

### **Effect 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 warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

Prandilin should be used with caution in athletes.

## **USE FOR PREGNANT WOMEN AND NURSING MOTHERS**

### **Pregnancy**

According to the literature, 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.

### **PEDIATRIC USE**

According to the literature, Clinical trials have been performed in children (61 patients aged 2 to 11) and children and adolescents (481 patients aged 9 to 19 years), comparing insulin lispro to human soluble insulin. The pharmacodynamic profile of insulin lispro in children is similar to that seen in adults.

Insulin lispro is approved for use in children for subcutaneous daily injection. Insulin lispro has not been studied neither in pediatric patients younger than 3 years of age nor in pediatric patients with type 2 diabetes.

As in adults, the dosage of insulin lispro must be individualized in pediatric patients based on metabolic needs and results of frequent monitoring of blood glucose.

### **GERIATRIC USE**

No special instructions. Please refer to **DOSAGE AND ADMINISTRATION**, or follow the doctor's advice.

### **DRUG INTERACTIONS**

Insulin requirements may be increased by medicinal products with hyperglycaemic 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 medicinal products 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.

The physician should be consulted when using other medications in addition to Prandilin.

### **OVERDOSAGE**

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.

## **PHARMACODYNAMICS**

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.

The primary activity of insulin lispro is the regulation of glucose metabolism by stimulating glucose uptake in peripheral tissues, especially by muscles and fat, and by inhibiting hepatic glucose production. Simultaneously insulin lispro inhibits lipolysis of adipocytes and proteolysis, and enhance protein synthesis.

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.

## **PHARMACOKINETICS**

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 pharmacokinetics of insulin lispro reflect a compound that is rapidly absorbed, and achieves peak blood levels 30 to 70 minutes following subcutaneous injection.

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.

## **STORAGE**

### Unopened cartridges

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

### In-use cartridges

Store below 30 °C. Do not refrigerate. The pen with the inserted cartridge should not be stored with the needle attached. Keep the cartridge in the outer carton in order to protect from light.

## **PACKAGE**

Cartridge, compound aluminum cap, brominated butyl rubber stopper, 1 cartridge/box

## **SHELF LIFE**

### Unopened cartridges

24 months

### In-use cartridges

28 days

## **MANUFACTURER**

Name: Gan & Lee Pharmaceuticals

Address: No. 8 Nanfeng West 1<sup>st</sup> Street, Huoxian, Tongzhou District, Beijing, China.

Postal code: 101109

Tel/Fax: +86 800 810 5020, +86 10 6050 4998

[Http://www.ganlee.com](http://www.ganlee.com)