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Insulin Lispro Mix 75/25 Injection

DRUG NAME

Generic name: Insulin Lispro Mix 75/25 Injection

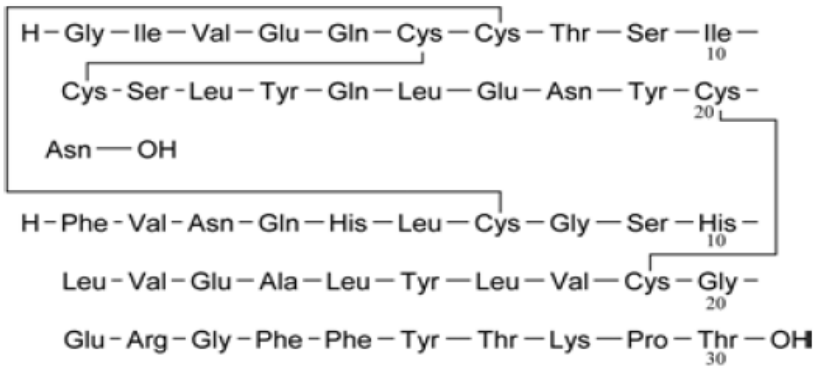
Trade name: Prandilin™ 25

COMPOSITION

Active ingredient: Insulin Lispro

Chemical name: 28^{B}-L-Lysine-29^{B}-L-proline insulin

Chemical structural formula:



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

Molecular weight: 5808 Da

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

DESCRIPTION

White and cloudy, sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

INDICATION

Prandilin 25 is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

STRENGTHS

100 units/mL in 3-mL cartridge

DOSAGE AND ADMINISTRATION

Usage:

Always use Prandilin 25 exactly as your doctor has told you. You should check with your doctor if you are not sure. To prevent the possible transmission of disease, each cartridge must be used by you only, even if the needle on the delivery device is changed.

When administered subcutaneously care should be taken when injecting Prandilin 25 to ensure that a blood vessel has not been entered. Patients must be educated to use the proper injection techniques.

First wash your hands, and disinfect the rubber membrane of the cartridge.

Please bring Prandilin 25 to room temperature before use and follow the injection steps described below:

(1) Cartridges containing Prandilin 25 should be rotated in the palms of the hands ten times and inverted 180° ten times immediately before use to resuspend insulin until it appears uniformly cloudy or milky. If not, repeat the above procedure until contents are mixed. 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 it a frosted appearance. Check each time you inject yourself.

(2) Please refer to the relevant reusable pen package insert, when using Prandilin 25 in conjunction with a reusable pen.

(3) Before you make an injection, clean your skin as you have been instructed. Inject under the skin, as you were taught. Prandilin 25 is injected under the skin (subcutaneously) of the upper arm, thigh, or stomach area (abdomen). Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized 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 25.

(5) As soon as you have done the injection, take the needle off the pen using the outer needle cap. This will keep the Prandilin 25 sterile and prevent leaking. It will also stop air going back into the pen and the needle clogging up. **Do not share your needles.** Do not share your pen. Replace the cap on your pen. Leave the cartridge in the pen.

Dosage:

You should normally inject Prandilin 25 within 15 minutes of a meal. If you need to, you can inject soon after a meal. But your doctor will have told you exactly how much to use, when to use it, and how often. Under no circumstances should Prandilin 25 be given intravenously.

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 Prandilin 25 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.

Paediatric population

Administration of Prandilin 25 to children below 12 years of age should be considered only in case of an expected benefit when compared to soluble insulin.

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: ≥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		

Hypoglycemia:

Hypoglycemia is the most common adverse reaction associated with insulins, including Prandilin 25. 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, or in patients who experience recurrent hypoglycemia.

Hypokalemia:

All insulin products, including Prandilin 25, 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 (thickening or pitting of the skin) 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.

CONTRAINDICATIONS

Prandilin 25 is contraindicated to patients with hypersensitivity to the insulin lispro or to any of the excipients listed in ***COMPOSITION***.

Prandilin 25 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.

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 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 Prandilin 25 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 25 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 25 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

Administration of Prandilin 25 to children below 12 years of age should be considered only in case of an expected benefit when compared to soluble insulin.

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 25.

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

The primary activity of insulin lispro mix 75/25 injectionis 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 ℃. 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 month

In-use cartridges

28 days

MANUFACTURER

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