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Humalog® Mix25
(25% insulin lispro and 75% insulin lispro protamine suspension) [rDNA origin]

Humalog® Mix50
(50% insulin lispro and 50% insulin lispro protamine suspension) [rDNA origin]

INN / USAN NAME AND PHARMACOTHERAPEUTIC GROUP

INN and USAN: Insulin lispro

Humalog Mix25 and Humalog Mix50

25% insulin lispro and 75% insulin lispro protamine suspension [rDNA origin] (Humalog Mix25) is a mixture of insulin lispro, a rapid-acting blood glucose lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose lowering agent.

50% insulin lispro and 50% insulin lispro protamine suspension [rDNA origin] (Humalog Mix50) is a mixture of insulin lispro, a rapid-acting blood glucose lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose lowering agent.

PHARMACEUTICAL FORM

Humalog Mix25 (25% insulin lispro and 75% insulin lispro protamine suspension) is available as a white suspension for parenteral administration in a concentration of 100 units/mL in 10 mL vials, 3 mL cartridges and 3 mL prefilled insulin delivery devices.

Humalog Mix50 (50% insulin lispro and 50% insulin lispro protamine suspension) is available as a white suspension for parenteral administration in a concentration of 100 units/mL in 10 mL vials, 3 mL cartridges and 3 mL prefilled insulin delivery devices.

CLINICAL INFORMATION

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 / Dosing and Method of Administration

The dosage of Humalog Mix25 and Humalog Mix50 are determined by the physician in accordance with the requirements of the patient.

The rapid onset of insulin lispro activity allows Humalog Mix25 and Humalog Mix50 to be given closer to a meal (within 15 minutes) when compared with insulin mixtures containing regular insulin (30 to 45 minutes before mealtime).

Humalog Mix25 and Humalog Mix50 should be given only by subcutaneous injection.

Humalog Mix25 and Humalog Mix50 should **not** be administered intravenously.

Subcutaneous administration should be in the upper arms, thighs, buttocks, or abdomen. Injection sites should be rotated so that the same site is not used more than approximately once a month. Care should be taken to ensure that a blood vessel has not been entered when injecting insulin. Patients must be educated to use proper injection techniques.

The safety and effectiveness of Humalog Mix25 and Humalog Mix50 in patients less than 18 years of age have not been established.

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 Special Precautions for Use

WARNINGS:

Humalog Mix25 and Humalog Mix50 differ from other insulin mixtures because the mixtures contain insulin lispro which has a rapid onset of action. Patients taking Humalog Mix25 or Humalog Mix50 may require a change in dosage compared to that used with their previous insulins.

Hypoglycemia: Hypoglycemia is the most common adverse effect of insulin products, including Humalog Mix25 and Humalog Mix50. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes or intensified diabetes control.

Changes in Insulin Therapy: Any change in insulin therapy should be made cautiously and only under medical supervision. Changes in insulin strength, brand (manufacturer), type (e.g., regular, NPH), species (beef, pork, beef-pork, human, human insulin analog), and/or method of manufacture may result in the need for a change in dosage.

PRECAUTIONS:

Illness or Emotional Disturbance: Insulin requirements may be increased during illness or emotional disturbance.

Renal or Hepatic Failure: Insulin requirements may be reduced in the presence of renal or hepatic failure.

Activity or Diet Changes: Adjustment of dose may also be necessary if patients experience changes in their physical activity or in their usual diet.

Interaction with Other Medicaments and Other Forms of Interaction

Insulin requirements may be increased by drugs with hyperglycemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy.

Insulin requirements may be reduced in the presence of drugs with hypoglycemic activity, such as oral hypoglycemic agents, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants (monoamine oxidase inhibitors).

The physician should be consulted when using other medications in addition to Humalog Mix25 and Humalog Mix50.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Like human insulin, in one year animal studies insulin lispro did not produce proliferative effects or tumors in organs and tissues when given at very high subcutaneous doses in chronic toxicity tests. Insulin lispro was not mutagenic in a series of *in vitro* and *in vivo* tests. In animal studies, there is no evidence of insulin lispro-induced fertility impairment.

Use During Pregnancy and Lactation

Clinical trials using Humalog Mix25 and Humalog Mix50 during pregnancy have not been performed. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

Patients who are lactating may require adjustments in insulin dose, diet, or both. It is not known if insulin lispro or insulin lispro protamine suspension is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human breast milk.

Undesirable Effects

CLINICAL TRIAL DATA:

Adverse events possibly associated with insulin include the following:

Body as a Whole—allergic reactions

Skin and Appendages—injection site reaction, lipodystrophy, pruritis, rash

Other—hypoglycemia

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 (see Precautions).

Local allergy in patients may occur as redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic allergy to insulin is less common but potentially more serious. Generalized allergy to insulin may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergic reaction may be life threatening.

Overdose

Insulin overdose may cause hypoglycemia with accompanying symptoms that may include listlessness, confusion, palpitations, sweating, vomiting, and headache.

Hypoglycemia may occur as a result of an excess of insulin activity relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary, because hypoglycemia may recur after apparent clinical recovery.

Effects on the Ability to Drive and Use Machines

The proper use of the correct therapeutic dose of insulins has no known effect on driving or the use of machinery. 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).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic and Pharmacokinetic Properties

Insulin lispro has been shown to be equipotent to human insulin on a molar basis. Studies in normal volunteers and patients with diabetes show that insulin lispro has a more rapid onset, an earlier peak, and a shorter duration of glucose-lowering activity than human regular insulin. The earlier onset of insulin lispro's activity at approximately 15 minutes after administration is directly related to its more rapid rate of absorption. This allows insulin lispro to be given closer to a meal (within 15 minutes) when compared to regular insulin (30 to 45 minutes before mealtime). The rate of insulin lispro absorption and, consequently, the onset of activity can be affected by injection site, and other variables.

Results of a glucose clamp study in healthy volunteers showed that the absorption and activity profiles of insulin lispro protamine suspension are similar to those of human insulin isophane suspension (NPH). The pharmacokinetic and pharmacodynamic profiles of Humalog Mix25 and Humalog Mix50 were investigated in a glucose clamp study. The rapid activity of insulin lispro was maintained within each mixture. In addition, each mixture demonstrated a distinct pharmacokinetic and glucodynamic profile.

The primary activity of insulin, Humalog Mix25 and Humalog Mix50, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

PHARMACEUTICAL PARTICULARS

List of Excipients

Humalog Mix25 and Humalog Mix50 contain glycerin, dibasic sodium phosphate, m-cresol, liquefied phenol, protamine sulfate, zinc oxide and water for injection, in addition to insulin lispro. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

Major Incompatibilities

The mixing of Humalog Mix25 and Humalog Mix50 with other insulins has not been studied.

Shelf Life

Two years when stored at 2°C to 8°C.

The in-use dating for Humalog Mix25 and Humalog Mix50 vials, cartridges and prefilled delivery devices is 28 days.

Special Precautions for Storage

Protect from sunlight. Store at refrigerated conditions (2°C to 8°C); do not freeze.

Instructions for Use/Handling

Re-suspension and administration instructions

Vials:
For vials, carefully shake or rotate the insulin bottle several times to completely mix the insulin. Insulin should look uniformly cloudy or milky after mixing. If not, repeat the above step until contents are mixed. Vials of insulin should be examined frequently. Do not use if the insulin substance (the white material) remains at the bottom of the vial after mixing. Do not use if there are clumps in the insulin after mixing. Do not use if the solid white particles stick to the bottom or wall of the vial, giving a frosted appearance. To administer insulin, use an insulin syringe marked for use with U100 insulins.

Cartridges:
For cartridges, roll the cartridge between the palms 10 times. Holding the cartridge by one end, invert it 180° slowly 10 times to allow the glass bead to travel the full length of the cartridge with each inversion. Insulin should look uniformly cloudy or milky after mixing. If not, repeat the above steps until the contents are mixed. Cartridges of insulin should be examined frequently. Do not use if the insulin substance (the white material) remains visibly separated from the liquid after mixing. Do not use if there are clumps in the insulin after mixing. Do not use if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance. To load the cartridge into the device and to attach the needle prior to administration of the insulin, refer to the manufacturer's instruction for the insulin delivery device. For instructions on how to administer insulin, refer to the manufacturer's instruction for the insulin delivery device.

Prefilled insulin delivery devices:
For prefilled insulin delivery devices, roll the device between the palms 10 times. Holding the device by one end, invert it 180° slowly 10 times to allow the glass bead to travel the full length of the cartridge with each inversion. Insulin should look uniformly cloudy or milky after mixing. If not, repeat the above steps until the contents are mixed. Prefilled insulin delivery devices should be examined frequently. Do not use if the insulin substance (the white material) remains visibly separated from the liquid after mixing. Do not use if there are clumps in the insulin after mixing. Do not use if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance. For instructions on how to administer insulin, refer to the manufacturer's instruction for the insulin delivery device.

Manufacturer
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