

Humalog® Mix25™

100 U/ml Pen suspension for injection

25% insulin lispro and

75% insulin lispro protamine suspension

(rDNA origin)



1. NAME OF THE MEDICINAL PRODUCT

Humalog Mix25 100 U/ml Pen, suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 100U (equivalent to 3.5mg) insulin lispro (recombinant DNA origin produced in E.coli). Each container includes 3ml equivalent to 300U insulin lispro.

Humalog Mix25 consists of 25% insulin lispro solution and 75% insulin lispro protamine suspension.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection. Humalog Mix25 is a white, sterile suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Humalog Mix25 is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

4.2 Posology and method of administration

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

Humalog Mix25 may be given shortly before meals. When necessary, Humalog Mix25 can be given soon after meals. Humalog Mix25 should only be given by subcutaneous injection. Under no circumstances should Humalog Mix25 be given intravenously.

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 Mix25 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 rapid onset and early peak of activity of Humalog itself is observed following the subcutaneous administration of Humalog Mix25. This allows Humalog Mix25 to be given very close to mealtime. The duration of action of the insulin lispro protamine suspension (NPL) component of Humalog Mix25 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 Humalog Mix25 is dependent on dose, site of injection, blood supply, temperature, and physical activity.

4.3 Contraindications

Hypoglycaemia.

Hypersensitivity to insulin lispro or to any of the excipients.

4.4 Special warnings and special precautions for use

Under no circumstances should Humalog Mix25 be given intravenously.

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.

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 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Insulin requirements may be increased by substances 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 substances with hypoglycaemic activity, such as oral hypoglycaemics, salicylates (for example, acetylsalicylic acid), sulpha antibiotics, certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme inhibitors (captopril, enalapril), beta-blockers, octreotide or alcohol.

Mixing Humalog Mix25 with other insulins has not been studied.

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

4.6 Pregnancy and lactation

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.

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

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 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 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

Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death.

Local allergy in patients occasionally occurs as redness, swelling, and itching 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, less common 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 may occur at the injection site.

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

Pharmaco-therapeutic group:

Humalog Mix25 is a premixed suspension consisting of insulin lispro (fast-acting human insulin analogue) and insulin lispro protamine suspension (intermediate acting human insulin analogue). ATC Code: A10A D04.

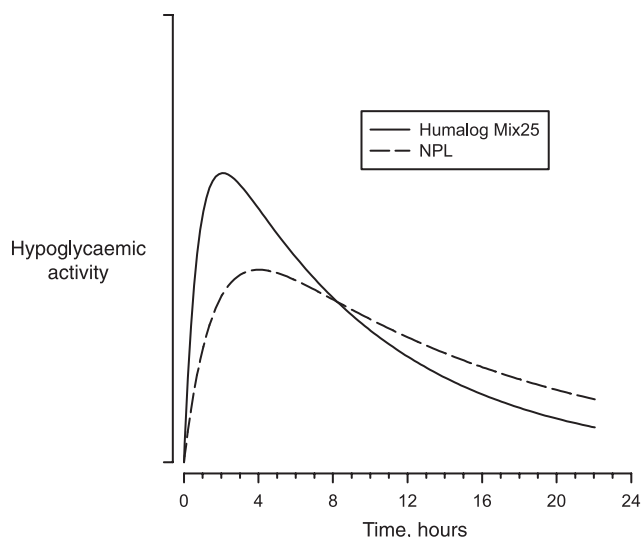
The primary activity of insulin lispro is the regulation of glucose metabolism.

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 regular insulin (30 to 45 minutes before). The rapid onset and early peak of activity of insulin lispro is observed following the subcutaneous administration of Humalog Mix25. NPL has an activity profile that is very similar to that of a basal insulin (NPH) over a period of approximately 15 hours.

Clinical trials in patients with type 1 and type 2 diabetes have demonstrated reduced postprandial hyperglycaemia with Humalog Mix25 compared to human insulin mixture 30/70. In one clinical study there was a small (0.38 mmol/l) increase in blood glucose levels at night (3a.m.).

In the figure below the pharmacodynamics of Humalog Mix25 and NPL 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 effect 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.

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. The pharmacokinetics of insulin lispro protamine suspension are consistent with those of an intermediate acting insulin such as NPH. The pharmacokinetics of Humalog Mix25 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 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.

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

Protamine sulphate, *m*-cresol [1.76 mg/ml], phenol [0.80 mg/ml], glycerol, dibasic sodium phosphate. 7H₂O, zinc oxide, water for injections. Hydrochloric acid and sodium hydroxide may be used to adjust pH to 7.0 – 7.8.

6.2 Incompatibilities

Mixing Humalog Mix25 with other insulins has not been studied. In the absence of compatibility studies, this medicinal product must not be mixed with another medicinal product.

6.3 Shelflife

Two years.

After first use of the pen, the suspension should be used within 28 days, when stored below + 30°C.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator).

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

Once in use pens may be used for up to 28 days.

6.5 Nature and contents of container

The suspension is contained in type I flint glass cartridges, sealed with halobutyl disc seals and plunger heads and secured with aluminium seals. Dimeticone or silicone emulsion may have been used to treat the cartridge plunger, and/or the glass cartridge. The 3 ml cartridges are sealed in a disposable pen injector, called the "Pen". Needles are not included.

Not all packs may be marketed in every country.

5 x 3 ml Humalog Mix25 100 U/ml Pens.

2 x (5 x 3 ml) Humalog Mix25 100 U/ml Pens.

6.6 Instructions for use, handling, and disposal (if appropriate)

a) Preparing a dose

1. Inspect the Humalog Mix25 100 U/ml Pen.

The Pen 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 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 a frosted appearance.

2. Put on the needle.

Wipe the rubber seal with alcohol. Remove the paper tab from the capped needle. Screw the capped needle clockwise onto the pen until it is tight. Hold the pen with needle pointing up and remove the outer needle cap and inner needle cover.

3. Priming Pen (check insulin flow).

- (a) The arrow should be visible in the dose window. If the arrow is not present, turn the dose knob clockwise until the arrow appears and notch is felt or visually aligned.
- (b) Pull dose knob out (in direction of the arrow) until a "0" appears in the dose window. A dose cannot be dialled until the dose knob is pulled out.
- (c) Turn dose knob clockwise until a "2" appears in the dose window.
- (d) Hold the pen with needle pointing up and tap the clear cartridge holder gently with your finger so any air bubbles collect near the top. Depress the injection button fully until you feel or hear a click. You should see a drop of insulin at the tip of the needle. If insulin does not appear, repeat the procedure until insulin appears.
- (e) Always prime the pen (check the insulin flow) before each injection. Failure to prime the pen may result in an inaccurate dose.

4. Setting the Dose.

- (a) Turn the dose knob clockwise until the arrow appears in the dose window and a notch is felt or visually aligned.
- (b) Pull the dose knob out (in the direction of the arrow) until a "0" appears in the dose window. A dose cannot be dialled until the dose knob is pulled out.
- (c) Turn the dose knob clockwise until the dose appears in the dose window. If too high a dose is dialled, turn the dose knob backward (anti-clockwise) until the correct dose appears in the window. A dose greater than the number of units remaining in the cartridge cannot be dialed.

b) Injecting a dose

1. Wash your hands.
 2. Choose a site for injection.
 3. Clean the skin as instructed.
 4. Remove outer needle cap.
 5. Stabilise the skin by spreading it or pinching up a large area. Insert the needle as instructed.
 6. Press the injection button down with the thumb (until you hear or feel a click); wait 5 seconds.
 7. Pull the needle out and apply gentle pressure over the injection site for several seconds. Do not rub the area.
 8. Immediately after an injection, use the outer needle cap to unscrew the needle. Remove the needle from the pen. This will ensure sterility, and prevent leakage, reentry of air, and potential needle clogs. Do not reuse the needle. Dispose of the needle in a responsible manner. Needles and pens must not be shared.
- The pre-filled pen can be used until it is empty. Please properly discard or recycle.
9. Replace the cap on the pen.
 10. Use of injection sites should be rotated so that the same site is not used more than approximately once a month.
 11. The injection button should be fully depressed before using the pen again.

7. DATE OF REVISION OF THE TEXT

April 7, 2005

Manufactured by:
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F-67640 Fegersheim, France