HUMALOG MIX 50

1. NAME OF THE MEDICINAL PRODUCT

Humalog Mix50 100 units/ml suspension for injection in

cartridge

2. Qualitative and quantitative composition

Each ml contains 100 units insulin lispro* (equivalent to 3.5mg).

Humalog Mix50 consists of 50% insulin lispro solution and 50% insulin lispro protamine suspension.
Each cartridge contains 300 units of insulin lispro in 3 ml suspension.

*produced in *E.coli* by recombinant DNA technology.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

White suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Humalog Mix50 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

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

Humalog Mix50 may be given shortly before meals. When necessary, Humalog Mix50 can be given soon after meals. Humalog Mix50 should only be given by subcutaneous injection. Under no circumstances should Humalog Mix50 be given intravenously.

The rapid onset and early peak of activity of Humalog itself is observed following the subcutaneous administration of Humalog Mix50. This allows Humalog Mix50 to be given very close to mealtime.
The duration of action of the insulin lispro protamine suspension component of Humalog Mix50 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 Mix50 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 Humalog Mix50 to children below 12 years of age should be considered only in case of an expected benefit when compared to soluble insulin.

Method of administration

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 Mix50 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.

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

Under no circumstances should Humalog Mix50 be given intravenously.

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 Humalog Mix50 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 Mix50 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.

Avoidance of medication errors
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 substances 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 substances 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.

Mixing Humalog Mix50 with other insulins has not been studied.

The physician should be consulted when using other medications in addition to Humalog Mix (see section 4.4).

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).

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

Summary of safety profile

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. 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		

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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

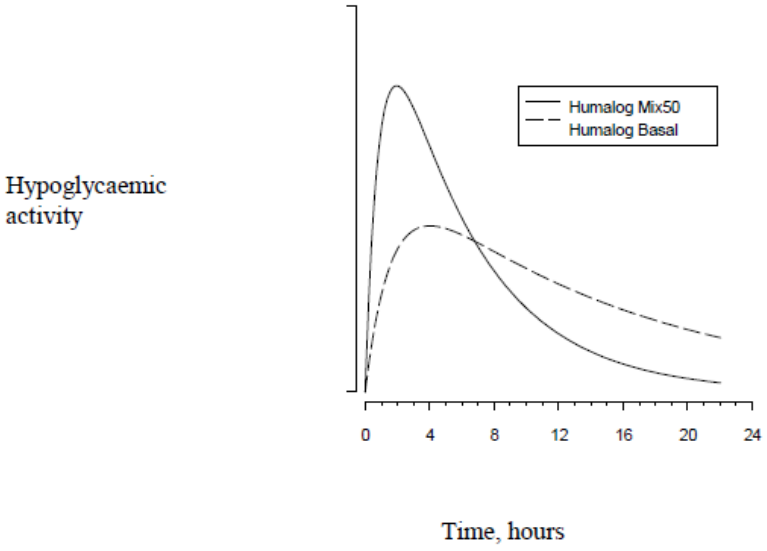
Pharmaco-therapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate or long acting combined with fast acting. ATC Code: A10A D04.

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 soluble 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 Mix50. Humalog basal has an activity profile that is very similar to that of a basal insulin (NPH) over a period of approximately 15 hours.

In the figure below the pharmacodynamics of Humalog MIX50 and BASAL 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 Mix50 are representatives 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, metaCresol, liquefied phenol, glycerol, dibasic sodium phosphate, zinc oxide, water for injection. hydrochloric acid solution 10% and sodium hydroxide solution 10% may be used to adjust pH.

6.2 Incompatibilities

Mixing Humalog Mix50 with other insulins has not been studied. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before use
The expiry date of the product is indicated on the packaging materials.

After cartridge insertion
28 days.

6.4 Special precautions for storage

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

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

After cartridge insertion
Store below 30°C. Do not refrigerate. The pen with the inserted cartridge should not be stored with the needle attached.

6.5 Nature and contents of container

Cartridge
The suspension is contained in type I flint glass cartridges, sealed with butyl or 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.

5 x 3 ml Humalog Mix50 Cartridges for a 3ml pen.

6.6 Special precautions for disposal and other handling

Instructions for use and handling
To prevent the possible transmission of disease, each cartridge must be used by one patient only, even if the needle on the delivery device is changed. The patient should discard the needle after every injection.

The Humalog Mix50 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 container, giving it a frosted appearance.

Preparing a dose

Cartridges containing Humalog Mix 50 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.

Humalog Mix50 cartridges are to be used with a Lilly reusable insulin pen and should not be used with any other reusable pen as the dosing accuracy has not been established with other pens.

The instructions with each individual pen must be followed for loading the cartridge, attaching the needle and administering the insulin injection.

Injecting a dose

If using a pre-filled or reusable pen refer to the detailed instructions for preparing the pen and injecting the dose, the following is a general description.

1. Wash your hands.
2. Choose a site for injection.
3. Clean the skin as instructed.
4. Stabilise the skin by spreading it or pinching up a large area. Insert the needle and inject as instructed.
5. Pull the needle out and apply gentle pressure over the injection site for several seconds. Do not rub the area.
6. Using the outer needle cap, unscrew the needle and dispose of it safely.
7. Use of injection sites should be rotated so that the same site is not used more than approximately once a month.

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

7. MANUFACTURER

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8. MANUFACTURING SITE

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9. LICENSE HOLDER

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The content of this leaflet was reviewed and approved by the Ministry of Health in April 2017, and was updated in accordance with the Ministry of Health's guidelines in February 2020.