

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Proprietary Medicinal Product

HUMALOG[®] vials (40 U/mL, 10 mL)
Insulin lispro

2. Qualitative and Quantitative Composition

HUMALOG[®] is a sterile, clear, colourless, aqueous solution of insulin lispro ([Lys (B28), Pro (B29)] human insulin analog, rDNA origin) adjusted to pH 7.0 - 7.8. The name insulin lispro is approved by INN, USAN and BAN

<u>Active Ingredient</u>	<u>Quantity per mL</u>
insulin lispro (recombinant DNA origin produced in <i>E. coli</i>)	40 U

The concentration of insulin lispro is 1.4mg insulin lispro per ml for the 40U/ml product.

3. Pharmaceutical Form

A solution for injection, in a 10 mL vial (40 U/mL of insulin lispro) to be used in conjunction with an appropriate syringe (40 U markings) for parenteral administration.

4. Clinical Particulars

4.1 Therapeutic Indication

For the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. HUMALOG[®] is also indicated for the initial stabilization of diabetes mellitus. HUMALOG[®] is a short acting insulin and may be used in conjunction with a longer acting human insulin. HUMALOG[®] is indicated for preprandial administration.

4.2 Posology and Method of Administration

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

HUMALOG[®] preparations should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection.

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.

Care should be taken when injecting HUMALOG[®] to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged.

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

HUMALOG[®] may be administered in conjunction with a longer acting human insulin, on the advice of a physician.

4.3 Contra-Indications

Hypoglycemia.

Hypersensitivity to insulin lispro or one of its excipients.

4.4 Special Warnings and Special Precautions for Use

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 analog), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

The shorter acting HUMALOG[®] should be drawn into the syringe first, to prevent contamination of the vial by the longer acting insulin. Mixing of the insulins ahead of time or just before the injection should be on advice of the physician. However, a consistent routine must be followed.

Patients taking HUMALOG[®] may require a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Patients whose blood glucose is greatly improved, e.g. by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycaemia and should be advised accordingly.

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.

Insulin requirements may be reduced in the presence of renal or hepatic impairment.

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 hypoglycemia.

4.5 Interaction with other Medicaments and other Forms of Interaction

Insulin requirements may be increased by drugs with hyperglycaemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy, danazol, beta 2 stimulants (ritrodine, salbutamol, terbutaline).

Insulin requirements may be reduced in the presence of drugs with hypoglycemic activity, such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants, certain angiotensin converting enzyme inhibitors (captopril, enalapril), beta blockers, octreotide, alcohol.

HUMALOG[®] should not be mixed with animal insulins.

The physician should be consulted when using other medications in addition to HUMALOG[®].

4.6 Use in Pregnancy and Lactation

There is no significant experience with HUMALOG[®] in pregnancy.

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.

4.6a There is no significant experience in children below 12 years of age.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

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.

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 generalized allergy to insulin. It may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized 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 or insulin lispro 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.

5. Pharmacological Properties

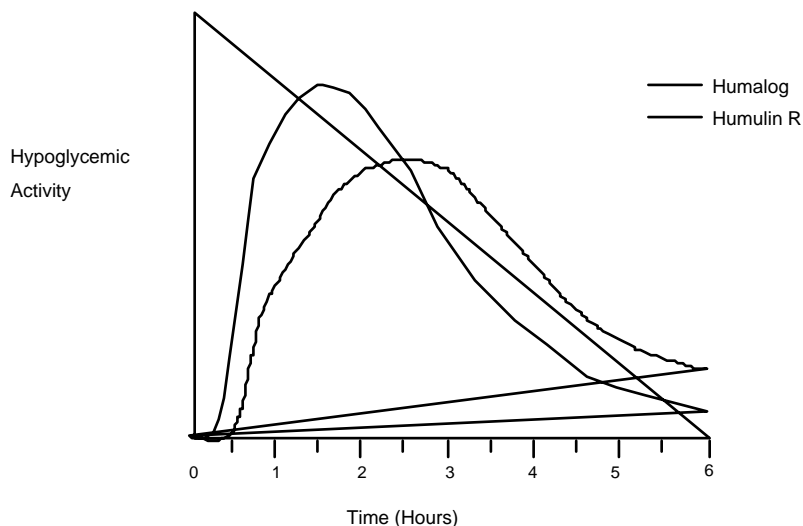
5.1 Pharmacodynamic Properties

Pharmaco-therapeutic group : fast acting human insulin analogue.

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, glyconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

HUMALOG[®] 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). HUMALOG[®] takes effect rapidly and has a shorter duration of activity (2 to 5 hours) when compared to regular insulin. As with all insulin preparations, the time course of HUMALOG[®] action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature and physical activity. The typical activity profile following subcutaneous injection is illustrated below.



The above representation reflects the relative amount of glucose over time required to maintain subject's whole blood glucose concentrations near fasting levels and is an indicator of the effect of these insulins on glucose metabolism over time.

5.2 Pharmacokinetic Properties

The pharmacokinetics of HUMALOG[®] reflect a compound that is rapidly absorbed, and achieves peak blood levels 30 to 70 minutes following subcutaneous injection. When considering the clinical relevance of these kinetics, it is more appropriate to examine the glucose utilization curves (as discussed in 5.1).

5.3 Preclinical Safety

In *in vitro* tests, including binding to insulin receptor sites and effects on growing cells, HUMALOG[®] behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of HUMALOG[®] is equivalent to human insulin. Acute, one month, and twelve month toxicology studies produced no significant toxicity findings.

6. Pharmaceutical Particulars

6.1 List of Excipients

Each vial will contain insulin lispro and the following excipients;
 (a) *m*-Cresol distilled [3.15mg/mL] (b) glycerol (c) dibasic sodium phosphate.7H₂O (d) zinc oxide
 (e) water for injection (f) hydrochloric acid and (g) sodium hydroxide.

These are included as;

(a) preservative and stabilizer (b) tonicity modifier (c) a buffering agent (d) stabilizer (e) a vehicle
 (f) pH adjustment and (g) pH adjustment respectively.

6.2 Incompatibilities

HUMALOG[®] preparations should not be mixed with animal insulin preparations.

6.3 Shelf-Life

Two years when stored under appropriate conditions. The in-use shelf-life is 28 days.

6.4 Special Precautions for Storage

HUMALOG[®] preparations should be stored in a refrigerator between 2° and 8°C. They should not be frozen or exposed to excessive heat or sunlight. If refrigeration is not possible, the vial being used can be kept at ambient temperature for up to 28 days, below 30°C and away from direct heat and light.

6.5 Nature and Content of Container

The solution is filled aseptically into Type I flint glass vials. The glass conforms to Ph Eur requirements. The containers are then sealed with butyl or halobutyl stoppers. Dimethicone or silicone emulsion may be used to treat the vial stopper. The closures are secured with aluminum seals.

6.6 Instructions for Use / Handling

a) Preparing a dose

Inspect the HUMALOG[®]. It should be clear and colourless. Do not use HUMALOG[®] if it appears cloudy, thickened, or slightly coloured or if solid particles are visible.

a) HUMALOG[®]

1. Wash your hands.
2. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper.
3. If the therapeutic regimen requires the injection of basal insulin and HUMALOG[®] at the same time, the two can be mixed in the syringe. If mixing insulins, refer to the instructions for mixing that follow in Section (b).
4. Draw air into the syringe equal to the prescribed HUMALOG[®] dose. Wipe the top of the bottle with an alcohol swab. Put the needle through rubber top of the HUMALOG[®] bottle and inject the air into the bottle.
5. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.
6. Making sure the tip of the needle is in the HUMALOG[®], withdraw the correct dose into the syringe.
7. Before removing the needle from the bottle, check the syringe for air bubbles that reduce the amount of HUMALOG[®] in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.

8. Remove the needle from the bottle and lay the syringe down so that the needle does not touch anything.

b) Mixing HUMALOG[®] with longer-acting Human Insulins

1. HUMALOG[®] should be mixed with longer-acting human insulins only on the advice of a doctor.
2. Draw air into the syringe equal to the amount of longer-acting insulin being taken. Insert the needle into the longer-acting insulin bottle and inject the air. Withdraw the needle.
3. Now inject air into the HUMALOG[®] bottle in the same manner, but **do not** withdraw the needle.
4. Turn the bottle and syringe upside down.
5. Making sure the tip of the needle is in the HUMALOG[®], withdraw the correct dose of HUMALOG[®] into the syringe.
6. Before removing the needle from the bottle, check the syringe for air bubbles that reduce the amount of HUMALOG[®] in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
7. Remove the needle from the bottle of HUMALOG[®] and insert it into the bottle of the longer-acting insulin. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand and shake gently. Making sure the tip of the needle is in the insulin, withdraw the dose of longer-acting insulin.
8. Remove the needle and lay the syringe down so that the needle does not touch anything.

c) Mixing Insulins

Do not mix insulins in vials with insulins in cartridges.

6.7 Name and Address of the Holder of the Marketing Authorization

The marketing authorization holder will be Eli Lilly Nederland B V., Krijtwal 17-23, 3432 ZT Nieuwegein, Netherlands.

7 Marketing Authorization Number

8 Date of Approval / Revision of SPC

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Proprietary Medicinal Product

HUMALOG[®] vials (100 U/mL, 10 mL)
Insulin lispro

2. Qualitative and Quantitative Composition

HUMALOG[®] is a sterile, clear, colourless, aqueous solution of insulin lispro ([Lys (B28), Pro (B29)] human insulin analog, rDNA origin) adjusted to pH 7.0 - 7.8. The name insulin lispro is approved by INN, USAN and BAN

<u>Active Ingredient</u>	<u>Quantity per mL</u>
insulin lispro (recombinant DNA origin produced in <i>E. coli</i>)	100 U

The concentration of insulin lispro is 3.5mg insulin lispro per ml for the 100 U/ml product.

3. Pharmaceutical Form

A solution for injection, in a 10 mL vial (100 U/mL of insulin lispro) to be used in conjunction with an appropriate syringe (100 U markings) for parenteral administration.

4. Clinical Particulars

4.1 Therapeutic Indication

For the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. HUMALOG[®] is also indicated for the initial stabilization of diabetes mellitus. HUMALOG[®] is a short acting insulin and may be used in conjunction with a longer acting human insulin. HUMALOG[®] is indicated for preprandial administration.

4.2 Posology and Method of Administration

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

HUMALOG[®] preparations should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection.

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.

Care should be taken when injecting HUMALOG[®] to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged.

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

HUMALOG[®] may be administered in conjunction with a longer acting human insulin, on the advice of a physician.

4.3 Contra-Indications

Hypoglycemia.

Hypersensitivity to insulin lispro or one of its excipients.

4.4 Special Warnings and Special Precautions for Use

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 analog), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

The shorter acting HUMALOG[®] should be drawn into the syringe first, to prevent contamination of the vial by the longer acting insulin. Mixing of the insulins ahead of time or just before the injection should be on advice of the physician. However, a consistent routine must be followed.

Patients taking HUMALOG[®] may require a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Patients whose blood glucose is greatly improved, e.g. by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycaemia and should be advised accordingly.

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.

Insulin requirements may be reduced in the presence of renal or hepatic impairment.

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 hypoglycemia.

4.5 Interaction with other Medicaments and other Forms of Interaction

Insulin requirements may be increased by drugs with hyperglycaemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy, danazol, beta 2 stimulants (ritrodine, salbutamol, terbutaline).

Insulin requirements may be reduced in the presence of drugs with hypoglycemic activity, such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants, certain angiotensin converting enzyme inhibitors (captopril, enalapril), beta blockers, octreotide, alcohol.

HUMALOG[®] should not be mixed with animal insulins.

The physician should be consulted when using other medications in addition to HUMALOG[®].

4.6 Use in Pregnancy and Lactation

There is no significant experience with HUMALOG[®] in pregnancy.

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.

4.6a There is no significant experience in children below 12 years of age.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

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.

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 generalized allergy to insulin. It may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized 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 or insulin lispro 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.

5. Pharmacological Properties

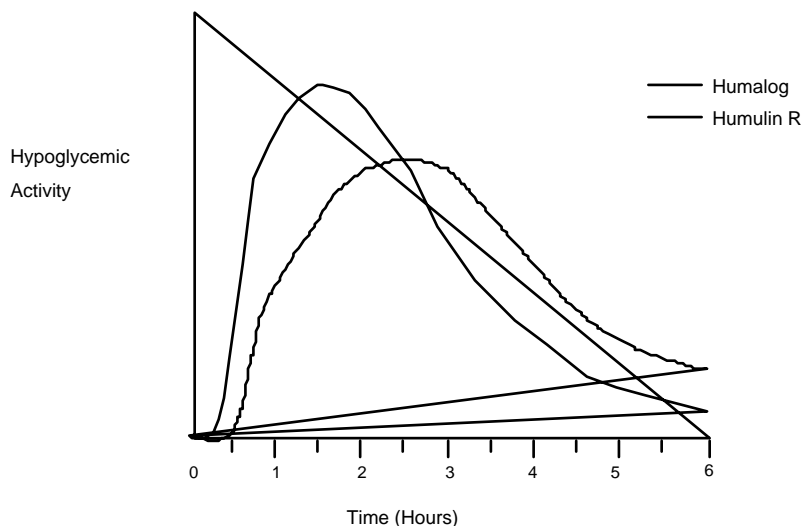
5.1 Pharmacodynamic Properties

Pharmaco-therapeutic group : fast acting human insulin analogue.

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, glyconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

HUMALOG[®] 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). HUMALOG[®] takes effect rapidly and has a shorter duration of activity (2 to 5 hours) when compared to regular insulin. As with all insulin preparations, the time course of HUMALOG[®] action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature and physical activity. The typical activity profile following subcutaneous injection is illustrated below.



The above representation reflects the relative amount of glucose over time required to maintain subject's whole blood glucose concentrations near fasting levels and is an indicator of the effect of these insulins on glucose metabolism over time.

5.2 Pharmacokinetic Properties

The pharmacokinetics of HUMALOG[®] reflect a compound that is rapidly absorbed, and achieves peak blood levels 30 to 70 minutes following subcutaneous injection. When considering the clinical relevance of these kinetics, it is more appropriate to examine the glucose utilization curves (as discussed in 5.1).

5.3 Preclinical Safety

In *in vitro* tests, including binding to insulin receptor sites and effects on growing cells, HUMALOG[®] behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of HUMALOG[®] is equivalent to human insulin. Acute, one month, and twelve month toxicology studies produced no significant toxicity findings.

6. Pharmaceutical Particulars

6.1 List of Excipients

Each vial will contain insulin lispro and the following excipients;
 (a) *m*-Cresol distilled [3.15mg/mL] (b) glycerol (c) dibasic sodium phosphate.7H₂O (d) zinc oxide
 (e) water for injection (f) hydrochloric acid and (g) sodium hydroxide.

These are included as;

(a) preservative and stabilizer (b) tonicity modifier (c) a buffering agent (d) stabilizer (e) a vehicle
 (f) pH adjustment and (g) pH adjustment respectively.

6.2 Incompatibilities

HUMALOG[®] preparations should not be mixed with animal insulin preparations.

6.3 Shelf-Life

Two years when stored under appropriate conditions. The in-use shelf-life is 28 days.

6.4 Special Precautions for Storage

HUMALOG[®] preparations should be stored in a refrigerator between 2° and 8°C. They should not be frozen or exposed to excessive heat or sunlight. If refrigeration is not possible, the vial being used can be kept at ambient temperature for up to 28 days, below 30°C and away from direct heat and light.

6.5 Nature and Content of Container

The solution is filled aseptically into Type I flint glass vials. The glass conforms to Ph Eur requirements. The containers are then sealed with butyl or halobutyl stoppers. Dimethicone or silicone emulsion may be used to treat the vial stopper. The closures are secured with aluminum seals.

6.6 Instructions for Use / Handling

a) Preparing a dose

Inspect the HUMALOG[®]. It should be clear and colourless. Do not use HUMALOG[®] if it appears cloudy, thickened, or slightly coloured or if solid particles are visible.

a) HUMALOG[®]

1. Wash your hands.
2. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper.
3. If the therapeutic regimen requires the injection of basal insulin and HUMALOG[®] at the same time, the two can be mixed in the syringe. If mixing insulins, refer to the instructions for mixing that follow in Section (b).
4. Draw air into the syringe equal to the prescribed HUMALOG[®] dose. Wipe the top of the bottle with an alcohol swab. Put the needle through rubber top of the HUMALOG[®] bottle and inject the air into the bottle.
5. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.
6. Making sure the tip of the needle is in the HUMALOG[®], withdraw the correct dose into the syringe.

7. Before removing the needle from the bottle, check the syringe for air bubbles that reduce the amount of HUMALOG[®] in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
 8. Remove the needle from the bottle and lay the syringe down so that the needle does not touch anything.
- b) Mixing HUMALOG[®] with longer-acting Human Insulins
1. HUMALOG[®] should be mixed with longer-acting human insulins only on the advice of a doctor.
 2. Draw air into the syringe equal to the amount of longer-acting insulin being taken. Insert the needle into the longer-acting insulin bottle and inject the air. Withdraw the needle.
 3. Now inject air into the HUMALOG[®] bottle in the same manner, but **do not** withdraw the needle.
 4. Turn the bottle and syringe upside down.
 5. Making sure the tip of the needle is in the HUMALOG[®], withdraw the correct dose of HUMALOG[®] into the syringe.
 6. Before removing the needle from the bottle, check the syringe for air bubbles that reduce the amount of HUMALOG[®] in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
 7. Remove the needle from the bottle of HUMALOG[®] and insert it into the bottle of the longer-acting insulin. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand and shake gently. Making sure the tip of the needle is in the insulin, withdraw the dose of longer-acting insulin.
 8. Remove the needle and lay the syringe down so that the needle does not touch anything.

c) Mixing Insulins

Do not mix insulins in vials with insulins in cartridges.

6.7 Name and Address of the Holder of the Marketing Authorization

The marketing authorization holder will be Eli Lilly Nederland B V., Krijtwal 17-23, 3432 ZT Nieuwegein, Netherlands.

7 Marketing Authorization Number

8 Date of Approval / Revision of SPC

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Proprietary Medicinal Product

HUMALOG[®] cartridge (100 U/mL, 1.5 mL)
Insulin lispro

2. Qualitative and Quantitative Composition

HUMALOG[®] is a sterile, clear, colourless, aqueous solution of insulin lispro ([Lys (B28), Pro (B29)] human insulin analog, rDNA origin) adjusted to pH 7.0 - 7.8. The name insulin lispro is approved by INN, USAN and BAN

<u>Active Ingredient</u>	<u>Quantity per mL</u>
insulin lispro (recombinant DNA origin produced in <i>E. coli</i>)	100 U

The concentration of insulin lispro is 3.5mg insulin lispro per ml for the 100 U/ml product.

3. Pharmaceutical Form

A solution for injection, in a 1.5 mL cartridge (100 U/mL of insulin lispro) to be used in conjunction with the B-D Pen Cartridge System, B-D Pen+ (B-D Pen Ultra), Lilly-Diapen I, or Lilly-Diapen II pen injection delivery systems for parenteral subcutaneous administration.

4. Clinical Particulars

4.1 Therapeutic Indication

For the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. HUMALOG[®] is also indicated for the initial stabilization of diabetes mellitus. HUMALOG[®] is a short acting insulin and may be used in conjunction with a longer acting human insulin. HUMALOG[®] is indicated for preprandial administration.

4.2 Posology and Method of Administration

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

HUMALOG[®] preparations should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection.

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.

Care should be taken when injecting HUMALOG[®] to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged.

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

HUMALOG[®] may be administered in conjunction with a longer acting human insulin, on the advice of a physician.

4.3 Contra-Indications

Hypoglycemia.

Hypersensitivity to insulin lispro or one of its excipients.

4.4 Special Warnings and Special Precautions for Use

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 analog), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

Patients taking HUMALOG[®] may require a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

Patients whose blood glucose is greatly improved, e.g. by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycaemia and should be advised accordingly.

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.

Insulin requirements may be reduced in the presence of renal or hepatic impairment.

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 hypoglycemia.

4.5 Interaction with other Medicaments and other Forms of Interaction

Insulin requirements may be increased by drugs with hyperglycaemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy, danazol, beta 2 stimulants (ritrodine, salbutamol, terbutaline).

Insulin requirements may be reduced in the presence of drugs with hypoglycemic activity, such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants, certain angiotensin converting enzyme inhibitors (captopril, enalapril), beta blockers, octreotide, alcohol.

HUMALOG[®] should not be mixed with animal insulins.

The physician should be consulted when using other medications in addition to HUMALOG[®].

4.6 Use in Pregnancy and Lactation

There is no significant experience with HUMALOG[®] in pregnancy.

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.

4.6a There is no significant experience in children below 12 years of age.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

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.

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 generalized allergy to insulin. It may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized 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 or insulin lispro 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.

5. Pharmacological Properties

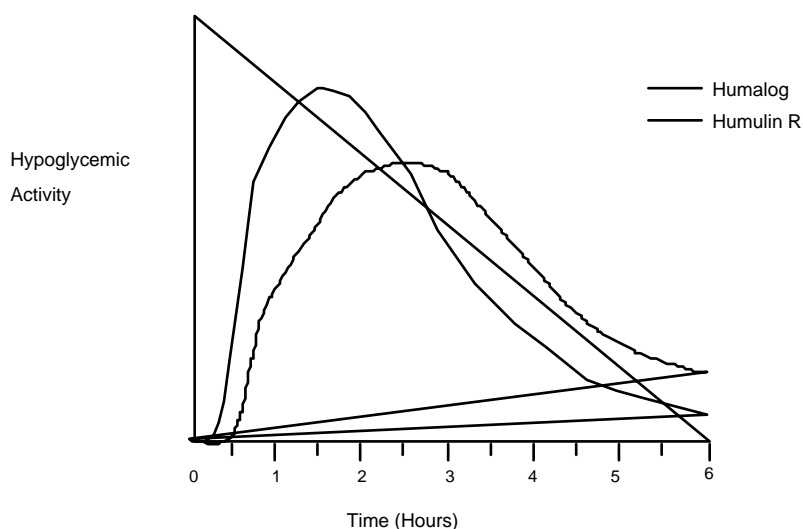
5.1 Pharmacodynamic Properties

Pharmaco-therapeutic group : fast acting human insulin analogue.

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, glyconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

HUMALOG[®] 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). HUMALOG[®] takes effect rapidly and has a shorter duration of activity (2 to 5 hours) when compared to regular insulin. As with all insulin preparations, the time course of HUMALOG[®] action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature and physical activity. The typical activity profile following subcutaneous injection is illustrated below.



The above representation reflects the relative amount of glucose over time required to maintain subject's whole blood glucose concentrations near fasting levels and is an indicator of the effect of these insulins on glucose metabolism over time.

5.2 Pharmacokinetic Properties

The pharmacokinetics of HUMALOG[®] reflect a compound that is rapidly absorbed, and achieves peak blood levels 30 to 70 minutes following subcutaneous injection. When considering the clinical relevance of these kinetics, it is more appropriate to examine the glucose utilization curves (as discussed in 5.1).

5.3 Preclinical Safety

In *in vitro* tests, including binding to insulin receptor sites and effects on growing cells, HUMALOG[®] behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of HUMALOG[®] is equivalent to human insulin. Acute, one month, and twelve month toxicology studies produced no significant toxicity findings.

6. Pharmaceutical Particulars

6.1 List of Excipients

Each cartridge will contain insulin lispro and the following excipients;
(a) *m*-Cresol distilled [3.15mg/mL] (b) glycerol (c) dibasic sodium phosphate.7H₂O (d) zinc oxide (e) water for injection (f) hydrochloric acid and (g) sodium hydroxide.
These are included as;
(a) preservative and stabilizer (b) tonicity modifier (c) a buffering agent (d) stabilizer (e) a vehicle (f) pH adjustment and (g) pH adjustment respectively.

6.2 Incompatibilities

HUMALOG[®] preparations should not be mixed with animal insulin preparations.

6.3 Shelf-Life

Two years when stored under appropriate conditions. The in-use shelf-life is 28 days.

6.4 Special Precautions for Storage

HUMALOG[®] preparations should be stored in a refrigerator between 2° and 8°C. They should not be frozen or exposed to excessive heat or sunlight. If refrigeration is not possible, the cartridge being used can be kept at ambient temperature for up to 28 days, below 30°C and away from direct heat and light. Following insertion in a pen, the cartridge and pen should not be refrigerated.

6.5 Nature and Content of Container

The solution is filled aseptically into Type I flint glass cartridges. The glass conforms to Ph Eur requirements. The containers are then sealed with butyl or halobutyl disk seals and plunger heads.

Dimethicone or silicone emulsion may be used to treat the cartridge plunger, and/or the glass cartridge. The closures are secured with aluminum seals.

6.6 Instructions for Use / Handling

a) Preparing a dose

Inspect the HUMALOG[®]. It should be clear and colourless. Do not use HUMALOG[®] if it appears cloudy, thickened, or slightly coloured or if solid particles are visible.

The manufacturer's instructions for the B-D Pen Cartridge System, B-D Pen+, (B-D Pen Ultra), Lilly-Diapen I, or Lilly-Diapen II pen injection delivery systems should be followed for loading the cartridge, attaching the needle and administering the insulin injection. The following description is a general one and the manufacturer's instructions with each individual pen must be followed.

b) Injecting a Dose

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

c) Mixing Insulins

Do not mix insulin in vials with insulin in cartridges

6.7 Name and Address of the Holder of the Marketing Authorization

The marketing authorization holder will be Eli Lilly Nederland B V., Krijtwal 17-23, 3432 ZT Nieuwegein, Netherlands.

7 Marketing Authorization Number

8 Date of Approval / Revision of SPC

ANNEX II

**MANUFACTURING AUTHORISATION AND CONDITIONS OF THE
MARKETING AUTHORISATION**

A. HOLDER(S) OF THE MANUFACTURING AUTHORISATION(S)

(Article 16 of Council Directive 75/319/EEC, as amended)

- Manufacturer of the active ingredient:
 - a) Fermentation and granule isolation: Dista Products Limited, Fleming Road, Speke Liverpool, L24 9LN, United Kingdom.
 - b) Responsible for importing after purification: Lilly France S.A., Rue du Colonel Lilly, 67640 Fegersheim, France.

- Manufacturing sites for the finished product:

Vials:

- a) Formulation, filling of finished product into unlabelled vials by Lilly France S.A., Rue du Colonel Lilly, 67640 Fegersheim, France.
- b) Labelling, packaging and batch release by Lilly Deutschland GmbH, Teichweg 335396, Giessen, Germany.

GMP certificates were issued by the French authorities on 28 April 1993 and by the German authorities on 23 June 1993.

Cartridges:

Formulation, filling into cartridges, labelling, finishing in blister packs and batch release by Lilly France S.A., Rue du Colonel Lilly, 67640 Fegersheim, France.

GMP certificate was issued by the French authorities on 28 April 1993

B) CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

(Articles 2 and 3 of Directive 92/26/EEC)

Medicinal product subject to renewable medical prescription

C) SPECIFIC OBLIGATIONS OF THE MARKETING AUTHORISATION HOLDER

The company has to provide to the EMEA additional information on the pharmaceutical dossier within the following timeframe:

1. The company will review and revise specifications of the drug substance and the finished product. The company will submit information one year after the marketing authorisation has been granted, unless fewer than 10 lots of the final product forms have been manufactured. If that is the case, the company will forthwith inform the EMEA as soon as 10 lots of each of the final forms (40 and 100 IU vials and 100IU cartridges) have been manufactured.

2. The company will submit updated 24 month stability data of ongoing studies by 1 April 1996.

Furthermore, for public health reasons, with a view to marketing in the Member States where insulin (vials) is not available at present in both concentrations (40 IU and 100 IU), until Community harmonisation has been implemented, the company must determine beforehand and in agreement with each national competent Authority, the conditions and timetable by which the other concentration may be sold.

ANNEX III

LABELLING AND USER PACKAGE LEAFLET

A - LABELLING

VIAL LABEL

Lilly

EC Authorization No.
10ml **VL-7514**

40 units per ml

Humalog®

insulin lispro (prb)

(rDNA origin)

For subcutaneous use

U-40

(1.4 mg/ml)

(EAN BAR CODE)

YL0XXX ZZZZZ

Use as directed by your doctor.

Important: Read the literature

Store between 2° and 8°C.

Avoid freezing.

Eli Lilly Nederland B.V.

Krijtwal 17-23

3432 ZT, Nieuwegein

The Netherlands

Exp. Date / Control No.

VIAL CARTON

Front

Lilly

EC Authorization No.
10ml **VL-7514**
40 units per ml

Humalog[®]
insulin lispro (prb)
(rDNA origin)

U-40
(1.4 mg/ml)

Back

U-40
(1.5 mg/ml)
Avoid freezing

VIAL CARTON (continued)

Side 1

Lilly

EC Authorization No.
10ml **VL-7514**
40 units per ml

Humalog[®]
insulin lispro (prb)
(rDNA origin)

U-40
(1.4 mg/ml)

Side 2

XX YYYY ZZZZZ

To be used as directed by your doctor or diabetes specialist nurse.

Store between 2° and 8°C.

Avoid freezing.

Keep out of reach of children.

For subcutaneous use.

Medicinal product subject to medical prescription.

See enclosed literature.

Contains glycerol, zinc oxide, dibasic sodium phosphate.7

H₂O with m-cresol as a preservative in water for injection.

Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust pH.

Eli Lilly Nederland B.V.
Krijtwal 17-23
3432 ZT, Nieuwegein
The Netherlands

VIAL CARTON (continued)

Top

U-40 10ml VL-7514

Humalog® *insulin lispro (prb)*

Exp. Date / Control No.

Bottom

Humalog®

insulin lispro (prb)

IMPORTANT: READ THE ENCLOSED LITERATURE.

VIAL LABEL

Lilly

EC Authorization No.
10ml **VL-7510**

100 units per ml

Humalog[®]

insulin lispro (prb)

(rDNA origin)

For subcutaneous use

U-100

(3.5 mg/ml)

(EAN BAR CODE)

YL0790 FSUKX

Use as directed by your doctor.

Important: Read the literature

Store between 2° and 8°C.

Avoid freezing.

Eli Lilly Nederland B.V.

Krijtwal 17-23

3432 ZT, Nieuwegein

The Netherlands

Exp. Date / Control No.

VIAL CARTON

Front

Lilly

EC Authorization No.
10ml **VL-7510**
100 units per ml

Humalog[®]
insulin lispro (prb)
(rDNA origin)

U-100
(3.5 mg/ml)

Back

U-100
(3.5 mg/ml)
Avoid freezing

VIAL CARTON (continued)

Side 1

Lilly

EC Authorization No.
10ml **VL-7510**
100 units per ml

Humalog®
insulin lispro (prb)
(rDNA origin)

U-100
(3.5 mg/ml)

Side 2

SH 8920 FSUKS

To be used as directed by your doctor or diabetes specialist nurse.

Store between 2° and 8°C.

Avoid freezing.

Keep out of reach of children.

For subcutaneous use.

Medicinal product subject to medicinal prescription.

See enclosed literature.

Contains glycerol, zinc oxide, dibasic sodium phosphate.7

H₂O with m-cresol as a preservative in water for injection.

Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust pH.

Eli Lilly Nederland B.V.
Krijtwal 17-23
3432 ZT, Nieuwegein
The Netherlands

VIAL CARTON (continued)

Top

U-100 10ml VL-7510

Humalog® *insulin lispro (prb)*

Exp. Date / Control No.

Bottom

Humalog®

insulin lispro (prb)

IMPORTANT: READ THE ENCLOSED LITERATURE.

CARTRIDGE LABEL

Lilly

EC Authorization No.

1.5ml VL-7515

100 units per ml

Humalog[®]

insulin lispro (prb)

(rDNA origin)

For subcutaneous use

YL0800 FSUKX

Exp. Date / Control No.

(EAN BAR CODE)

CARTRIDGE CARTON

Front

Lilly

EC Authorization No.
1.5ml VL-7515
100 units per ml

Humalog®
insulin lispro (prb)
(rDNA origin)

Back

CARTON HAS BEEN OPENED

To be used as directed by your doctor or diabetes specialist nurse.
Store between 2° and 8°. Avoid freezing. When in use, cartridges may be kept at room temperature (below 30°C) for up to 28 days, but do not expose to direct sunlight or excessive heat. Cartridges in use should not be refrigerated.

Keep out of reach of children.

For subcutaneous use.

Medicinal product subject to medical prescription.

See enclosed literature.

Contains glycerol, zinc oxide, dibasic sodium phosphate.7 H₂O with m-cresol as a preservative in water for injection.

Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust pH.

Lilly

Eli Lilly Nederland B.V.
Krijtval 17-23, 3432 ZT, Nieuwegein
The Netherlands

SH 8930 FSUKS

CARTRIDGE CARTON (continued)

Side 1

Lilly

5 X 1.5 ml cartridges 100 units per ml

U-100
(3.5 mg/ml)

Humalog® *insulin lispro (prb)*

Side 2

Lilly

5 X 1.5 ml cartridges 100 units per ml

U-100
(3.5 mg/ml)

Humalog® *insulin lispro (prb)*

Top

Exp. Date / Control No.

í To open, lift here and pull

1 **Humalog®** *insulin lispro (prb)*

IMPORTANT: READ THE ENCLOSED LITERATURE

Bottom

Lilly

5 X 1.5 ml cartridges 100 units per ml
Humalog® *insulin lispro (prb)*

U-100
(3.5 mg/ml)

B - USER PACKAGE LEAFLET

Humalog[®] (insulin lispro)

What you should know about Humalog[®] in vials

Please read this leaflet carefully before you start to use Humalog[®]. This leaflet does not contain all the information about Humalog[®] that you may need to know, so please ask your doctor, pharmacist or diabetes nurse specialist if you have any questions. This leaflet only applies to Humalog[®] vials.

What is in Humalog[®]?

Your medicine is called Humalog[®] and is used to treat diabetes. Its active ingredient is insulin lispro. This is a man-made form of human insulin. It works more quickly than normal human insulin because the insulin molecule has been changed slightly. You should normally use Humalog[®] within the 15 minutes before a meal. Its strength is 40 units per millilitre (U-40), and each bottle contains 400 units (10 millilitres).

Humalog[®] also contains the inactive ingredients m-cresol, glycerol, dibasic sodium phosphate. 7 H₂O, zinc oxide and water for injection. Sodium hydroxide and / or hydrochloric acid may have been used during manufacture to adjust pH.

PACK SHOT

Always check the pack and the bottle label for the name and type of the insulin when you get it from your pharmacy. Make sure you get the Humalog[®] that your doctor has told you to use.

Humalog[®] is made in the laboratory by a 'recombinant DNA technology' process. It is a changed form of human insulin and is therefore different from other human insulins and from animal source insulins. Human insulin, to which it is closely related, is a natural hormone and is made by the body's pancreas.

Humalog[®] is made by Lilly Deutschland GmbH, Teichweg 335396, Giessen, Germany. The product licence is held by Eli Lilly Nederland B.V., Krijtwal 17-23, 3432 ZT Nieuwegein, Netherlands.

Why Humalog[®]?

You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood. Humalog[®] is a substitute for your own insulin when you develop diabetes and is used to provide control in the long term. It works very quickly and for a shorter time than a soluble insulin.

Your doctor may tell you to use Humalog[®] with a longer-acting human insulin. Each of these comes with another patient information leaflet to tell you about them. Do not change your insulin unless your doctor or nurse tells you to. Be very careful if you do change insulin.

Before you inject Humalog[®]

Make sure it is safe for you to use Humalog[®].

• IF YOU THINK A ‘HYPO’ (LOW BLOOD SUGAR) IS STARTING, DO NOT INJECT HUMALOG[®] and do not drive. The back of this leaflet tells you how to deal with a mild ‘hypo’.

- If you have ever had an allergic reaction to Humalog[®] (see section D on the back of this leaflet), tell your doctor, pharmacist or diabetes nurse specialist.
- If your blood sugar levels are well controlled by your current insulin therapy, you may not feel the warning symptoms (see the back of the leaflet) when your blood sugar is falling too low. You must think carefully about when to have your meals, how often to exercise, and how much to do. You must also keep a close watch on your blood sugar levels by testing your blood glucose often.
- A few patients who have had ‘hypos’ after switching from animal insulin to human insulin have reported that the early warning symptoms were less obvious or different. If you often have ‘hypos’ or have difficulty recognising them, please discuss this with your doctor.

If you answer YES to any of the following questions, tell your doctor, pharmacist or diabetes nurse specialist.

- Have you recently become ill?
- Are you taking **any** other medicines? Your insulin needs may change if you are taking the contraceptive pill, steroids, thyroid hormone replacement therapy, oral hypoglycaemics, aspirin, sulfa antibiotics, octreotide, “beta-2 stimulants” (e.g. ritodrine, salbutamol or terbutaline), some antidepressants.
- Do you have trouble with your kidneys or liver?
- Are you exercising more than usual?
- Are you pregnant or contemplating becoming pregnant, or are you breast-feeding? Insulin requirements usually fall during the first three months of pregnancy and increase for the remainder. If you are breast feeding, insulin and or diet may require adjustment.
- Is the patient a child under 12 years old?

Your insulin needs may also change if you drink alcohol.

You should also tell your doctor, pharmacist or diabetes nurse specialist if you are planning to go abroad. The time difference between countries may mean that you have to have your injections and meals at different times from when you are at home.

Please read the back of this leaflet

What you should know about Humalog[®] in vials

Using Humalog[®] Dosage

You should normally inject Humalog[®] within 15 minutes before a meal. But your doctor will have told you exactly how much to use, when to use it, and how often. These instructions are only for you. Follow them exactly and visit your diabetes clinic regularly.

- If you change the type of insulin you use (for example from a human or animal insulin to Humalog[®]), you may have to take more or less than before. This might just be for the first injection or it may be a gradual change over several weeks or months.
- Inject Humalog[®] under the skin. You should only inject it into a muscle if your doctor has told you to.

Preparing Humalog[®]

- Humalog[®] is already dissolved in water, so you do not need to mix it. But you must use it **only** if it looks like water. It must be clear, have no colour and no solid pieces in it. Check this before each injection.

Injecting Humalog[®]

- First wash your hands.
- Clean your skin well where you are going to make the injection. Clean the rubber stopper on the bottle, but do not remove the stopper.
- Use a clean, sterile syringe and needle to pierce the rubber stopper and draw in the amount of Humalog[®] you want. Your doctor or clinic will tell you how to do this. **Do not share your needles and syringes.**
- Inject under the skin, as you were taught. Do not inject directly into a vein.
Do not rub the area you have just injected.
Make sure you inject at least half an inch (1cm) from the last injection and that you 'rotate' the places you inject, as you have been taught.
- Your doctor will tell you if you have to mix Humalog[®] with one of the human insulins. For example if you do need to inject a mixture, draw the Humalog[®] into the syringe before the long acting insulin. Inject the liquid as soon as you have mixed it. Do the same thing every time. You should not normally mix Humalog[®] with one of the mixtures of human insulins. You should never mix Humalog[®] with animal insulins.

- **Emergencies and overdoses:** If your blood sugar is low, eat glucose tablets or sugar followed by fruit or biscuits, and then rest. This will often get you over a mild ‘hypo’ or minor insulin overdose. If you get worse and your breathing is shallow and your skin gets pale, tell your doctor at once. A glucagon injection can treat quite severe hypoglycaemia. Eat glucose or sugar after the glucagon injection. If you do not respond to glucagon, you will have to be treated in hospital. Ask your doctor to tell you about glucagon.

If ‘hypos’ or ‘hypers’ (see A and B) are not treated they can be very serious and cause headaches, nausea, vomiting, dehydration, unconsciousness, coma or even death.

- Always keep spare syringes and a spare bottle of Humalog[®].
- Always carry something to show you are diabetic.
- Always carry sugar with you.

While using your insulin

Common problems of diabetes

A. Hypoglycaemia (‘hypo’ - low blood sugar) means there is not enough sugar in the blood. This can be caused if:

- you take too much Humalog[®] or other insulin;
- you miss or delay meals or change your diet;
- you exercise or work too hard just before or after a meal;
- you have an infection or illness (especially diarrhoea or vomiting);
- there is a change in your need for insulin; or
- you have trouble with your kidney or liver which gets worse

Alcohol and some medicines can affect your blood sugar levels.

The first symptoms of low blood sugar usually come on quickly and include:

- | | |
|---------------------------|------------------|
| •tiredness | •rapid heartbeat |
| •nervousness or shakiness | •nausea |
| •a headache | •cold sweat. |

B. Hyperglycaemia and diabetic ketoacidosis

Hyperglycaemia ('hyper'-too much sugar in the blood) means that your body does not have enough insulin. Hyperglycaemia can be brought about by:

- not taking your Humalog[®] or other insulin;
- taking less insulin than your doctor tells you to;
- eating a lot more than your diet allows; or
- fever, infection or emotional stress.

Hyperglycaemia can lead to diabetic ketoacidosis. The first symptoms come on slowly over many hours or days. They are:

- sleepy feeling
- no appetite
- flushed face
- fruity smell on the breath
- thirst
- feeling or being sick.

Severe symptoms are heavy breathing and a rapid pulse.

Get medical help immediately.

C. Illness

If you are ill, especially if you feel sick or are sick, your insulin needs may change. **Even when you are not eating normally, you still need insulin.** Test your urine or blood, follow your 'sick rules', and tell your doctor.

D. Allergy to insulin

Local allergy: Some people get redness, swelling or itching around the area of the insulin injection. This usually clears up in anything from a few days to a few weeks. If this happens to you, tell your doctor.

Systemic allergy: This allergy to insulin is not common. The symptoms are:

- rash over the whole body
- blood pressure dropping
- difficulty in breathing
- heart beating fast
- wheezing
- sweating.

If you think you are having this sort of insulin allergy with Humalog[®], tell your doctor at once.

E. Lipodystrophy

If you notice your skin thickening or pitting at the injection site, tell your doctor.

If you have these or any other side effects, tell your doctor.

How to store Humalog[®]

Keep your Humalog[®] in a fridge at between 2°-8°C. Do not put it near heat or in the sun. Do not freeze Humalog[®]. If you cannot keep your Humalog[®] in the fridge, you can keep it for up to 28 days at room temperature (up to 30°C). Keep your medicine where children cannot see or reach it. Do not use it after the 'Use before' date.

Remember: This medicine is for you. Never give it to others. It may harm them, even if their symptoms are the same as yours.

F. Date this leaflet was written

Humalog[®] (insulin lispro)

What you should know about Humalog[®] in vials

Please read this leaflet carefully before you start to use Humalog[®]. This leaflet does not contain all the information about Humalog[®] that you may need to know, so please ask your doctor, pharmacist or diabetes nurse specialist if you have any questions. This leaflet only applies to Humalog[®] vials.

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Your medicine is called Humalog[®] and is used to treat diabetes. Its active ingredient is insulin lispro. This is a man-made form of human insulin. It works more quickly than normal human insulin because the insulin molecule has been changed slightly. You should normally use Humalog[®] within the 15 minutes before a meal. Its strength is 100 units per millilitre (U-100), and each bottle contains 1000 units (10 millilitres).

Humalog[®] also contains the inactive ingredients m-cresol, glycerol, dibasic sodium phosphate. 7 H₂O, zinc oxide and water for injection. Sodium hydroxide and / or hydrochloric acid may have been used during manufacture to adjust pH.

PACK SHOT

Always check the pack and the bottle label for the name and type of the insulin when you get it from your pharmacy. Make sure you get the Humalog[®] that your doctor has told you to use.

Humalog[®] is made in the laboratory by a 'recombinant DNA technology' process. It is a changed form of human insulin and is therefore different from other human insulins and from animal source insulins. Human insulin, to which it is closely related, is a natural hormone and is made by the body's pancreas.

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You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood. Humalog[®] is a substitute for your own insulin when you develop diabetes and is used to provide control in the long term. It works very quickly and for a shorter time than a soluble insulin.

Your doctor may tell you to use Humalog[®] with a longer-acting human insulin. Each of these comes with another patient information leaflet to tell you about them. Do not change your insulin unless your doctor or nurse tells you to. Be very careful if you do change insulin.

Before you inject Humalog[®]

Make sure it is safe for you to use Humalog[®].

- **IF YOU THINK A ‘HYPO’ (LOW BLOOD SUGAR) IS STARTING, DO NOT INJECT HUMALOG[®]** and do not drive. The back of this leaflet tells you how to deal with a mild ‘hypo’.

- If you have ever had an allergic reaction to Humalog[®] (see section D on the back of this leaflet), tell your doctor, pharmacist or diabetes nurse specialist.

- If your blood sugar levels are well controlled by your current insulin therapy, you may not feel the warning symptoms (see the back of the leaflet) when your blood sugar is falling too low. You must think carefully about when to have your meals, how often to exercise, and how much to do. You must also keep a close watch on your blood sugar levels by testing your blood glucose often.

- A few patients who have had ‘hypos’ after switching from animal insulin to human insulin have reported that the early warning symptoms were less obvious or different. If you often have ‘hypos’ or have difficulty recognising them, please discuss this with your doctor.

If you answer YES to any of the following questions, tell your doctor, pharmacist or diabetes nurse specialist.

- Have you recently become ill?

- Are you taking **any** other medicines? Your insulin needs may change if you are taking the contraceptive pill, steroids, thyroid hormone replacement therapy, oral hypoglycaemics, aspirin, sulfa antibiotics, octreotide, “beta-2 stimulants” (e.g. ritodrine, salbutamol or terbutaline), some antidepressants.

- Do you have trouble with your kidneys or liver?

- Are you exercising more than usual?

- Are you pregnant or contemplating becoming pregnant, or are you breast-feeding? Insulin requirements usually fall during the first three months of pregnancy and increase for the remainder. If you are breast feeding, insulin and or diet may require adjustment

- Is the patient a child under 12 years old?

Your insulin needs may also change if you drink alcohol.

You should also tell your doctor, pharmacist or diabetes nurse specialist if you are planning to go abroad. The time difference between countries may mean that you have to have your injections and meals at different times from when you are at home.

Please read the back of this leaflet

What you should know about Humalog[®] in vials

Using Humalog[®] Dosage

You should normally inject Humalog[®] within 15 minutes before a meal. But your doctor will have told you exactly how much to use, when to use it, and how often. These instructions are only for you. Follow them exactly and visit your diabetes clinic regularly.

- If you change the type of insulin you use (for example from a human or animal insulin to Humalog[®]), you may have to take more or less than before. This might just be for the first injection or it may be a gradual change over several weeks or months.
- Inject Humalog[®] under the skin. You should only inject it into a muscle if your doctor has told you to.

Preparing Humalog[®]

- Humalog[®] is already dissolved in water, so you do not need to mix it. But you must use it **only** if it looks like water. It must be clear, have no colour and no solid pieces in it. Check this before each injection.

Injecting Humalog[®]

- First wash your hands.
- Clean your skin well where you are going to make the injection. Clean the rubber stopper on the bottle, but do not remove the stopper.
- Use a clean, sterile syringe and needle to pierce the rubber stopper and draw in the amount of Humalog[®] you want. Your doctor or clinic will tell you how to do this. **Do not share your needles and syringes.**
- Inject under the skin, as you were taught. Do not inject directly into a vein.
Do not rub the area you have just injected.
Make sure you inject at least half an inch (1cm) from the last injection and that you 'rotate' the places you inject, as you have been taught.
- Your doctor will tell you if you have to mix Humalog[®] with one of the human insulins. For example if you do need to inject a mixture, draw the Humalog[®] into the syringe before the long acting insulin. Inject the liquid as soon as you have mixed it. Do the same thing every time. You should not normally mix Humalog[®] with one of the mixtures of human insulins. You should never mix Humalog[®] with animal insulins.

• **Emergencies and overdoses:** If your blood sugar is low, eat glucose tablets or sugar followed by fruit or biscuits, and then rest. This will often get you over a mild ‘hypo’ or minor insulin overdose. If you get worse and your breathing is shallow and your skin gets pale, tell your doctor at once. A glucagon injection can treat quite severe hypoglycaemia. Eat glucose or sugar after the glucagon injection. If you do not respond to glucagon, you will have to be treated in hospital. Ask your doctor to tell you about glucagon.

If ‘hypos’ or ‘hypers’ (see A and B) are not treated they can be very serious and cause headaches, nausea, vomiting, dehydration, unconsciousness, coma or even death.

- Always keep spare syringes and a spare bottle of Humalog[®].
- Always carry something to show you are diabetic.
- Always carry sugar with you.

While using your insulin

Common problems of diabetes

A. Hypoglycaemia (‘hypo’ - low blood sugar) means there is not enough sugar in the blood. This can be caused if:

- you take too much Humalog[®] or other insulin;
- you miss or delay meals or change your diet;
- you exercise or work too hard just before or after a meal;
- you have an infection or illness (especially diarrhoea or vomiting);
- there is a change in your need for insulin; or
- you have trouble with your kidney or liver which gets worse

Alcohol and some medicines can affect your blood sugar levels.

The first symptoms of low blood sugar usually come on quickly and include:

- | | |
|---------------------------|------------------|
| •tiredness | •rapid heartbeat |
| •nervousness or shakiness | •nausea |
| •a headache | •cold sweat. |

B. Hyperglycaemia and diabetic ketoacidosis

Hyperglycaemia ('hyper'-too much sugar in the blood) means that your body does not have enough insulin. Hyperglycaemia can be brought about by:

- not taking your Humalog[®] or other insulin;
- taking less insulin than your doctor tells you to;
- eating a lot more than your diet allows; or
- fever, infection or emotional stress.

Hyperglycaemia can lead to diabetic ketoacidosis. The first symptoms come on slowly over many hours or days. They are:

- sleepy feeling
- no appetite
- flushed face
- fruity smell on the breath
- thirst
- feeling or being sick.

Severe symptoms are heavy breathing and a rapid pulse.

Get medical help immediately.

C. Illness

If you are ill, especially if you feel sick or are sick, your insulin needs may change. **Even when you are not eating normally, you still need insulin.** Test your urine or blood, follow your 'sick rules', and tell your doctor.

D. Allergy to insulin

Local allergy: Some people get redness, swelling or itching around the area of the insulin injection. This usually clears up in anything from a few days to a few weeks. If this happens to you, tell your doctor.

Systemic allergy: This allergy to insulin is not common. The symptoms are:

- rash over the whole body
- blood pressure dropping
- difficulty in breathing
- heart beating fast
- wheezing
- sweating.

If you think you are having this sort of insulin allergy with Humalog[®], tell your doctor at once.

E. Lipodystrophy

If you notice your skin thickening or pitting at the injection site, tell your doctor.

If you have these or any other side effects, tell your doctor.

How to store Humalog[®]

Keep your Humalog[®] in a fridge at between 2°-8°C. Do not put it near heat or in the sun. Do not freeze Humalog[®]. If you cannot keep your Humalog[®] in the fridge, you can keep it for up to 28 days at room temperature (up to 30°C). Keep your medicine where children cannot see or reach it. Do not use it after the 'Use before' date.

Remember: This medicine is for you. Never give it to others. It may harm them, even if their symptoms are the same as yours.

F.Date this leaflet was written

Humalog[®] (insulin lispro)

What you should know about Humalog[®] in cartridges

Please read this leaflet carefully before you start to use Humalog[®]. This leaflet does not contain all the information about Humalog[®] that you may need to know, so please ask your doctor, pharmacist or diabetes nurse specialist if you have any questions. This leaflet only applies to Humalog[®] cartridges.

What is in Humalog[®]?

Your medicine is called Humalog[®] and is used to treat diabetes. Its active ingredient is insulin lispro. This is a man-made form of human insulin. It works more quickly than normal human insulin because the insulin molecule has been changed slightly. You should normally use Humalog[®] within the 15 minutes before a meal. Its strength is 100 units per millilitre (U-100), and each cartridge contains 150 units (1.5 millilitre).

Humalog[®] also contains the inactive ingredients m-cresol, glycerol, dibasic sodium phosphate. 7 H₂O, zinc oxide and water for injection. Sodium hydroxide and / or hydrochloric acid may have been used during manufacture to adjust pH.

PACK SHOT

Always check the pack and the cartridge label for the name and type of the insulin when you get it from your pharmacy. Make sure you get the Humalog[®] that your doctor has told you to use.

Humalog[®] is made in the laboratory by a 'recombinant DNA technology' process. It is a changed form of human insulin and is therefore different from other human insulins and from animal source insulins. Human insulin, to which it is closely related, is a natural hormone and is made by the body's pancreas.

Humalog[®] is made by Lilly France SA, Rue du Colonel Lilly, 67640 Fegersheim, France. The product licence is held by Eli Lilly Nederland B.V., Krijtval 17-23, 3432 ZT Nieuwegein, Netherlands.

Why Humalog[®]?

You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood. Humalog[®] is a substitute for your own insulin when you develop diabetes and is used to provide control in the long term. It works very quickly and for a shorter time than a soluble insulin.

Your doctor may tell you to use Humalog[®] with a longer-acting human insulin. Each of these comes with another patient information leaflet to tell you about them. Do not change your insulin unless your doctor or nurse tells you to. Be very careful if you do change insulin.

Before you inject Humalog[®]

Make sure it is safe for you to use Humalog[®].

•IF YOU THINK A ‘HYPO’ (LOW BLOOD SUGAR) IS STARTING, DO NOT INJECT HUMALOG[®] and do not drive. The back of this leaflet tells you how to deal with a mild ‘hypo’.

•If you have ever had an allergic reaction to Humalog[®] (see section D on the back of this leaflet) tell your doctor, pharmacist or diabetes nurse specialist.

•If your blood sugar levels are well controlled by your current insulin therapy, you may not feel the warning symptoms (see the back of the leaflet) when your blood sugar is falling too low. You must think carefully about when to have your meals, how often to exercise and how much to do. You must also keep a close watch on your blood sugar levels by testing your blood glucose often.

•A few patients who have had ‘hypos’ after switching from animal insulin to human insulin have reported that the early warning symptoms were less obvious or different. If you often have ‘hypos’ or have difficulty recognising them, please discuss this with your doctor.

If you answer YES to any of the following questions, tell your doctor, pharmacist or diabetes nurse specialist.

•Have you recently become ill?

•Are you taking **any** other medicines? Your insulin needs may change if you are taking the contraceptive pill, steroids, thyroid hormone replacement therapy, oral hypoglycaemics, aspirin, sulfa antibiotics, octreotide, “beta-2 stimulants” (e.g. ritodrine, salbutamol or terbutaline) or some antidepressants.

•Do you have trouble with your kidneys or liver?

•Are you exercising more than usual?

•Are you pregnant or contemplating becoming pregnant, or are you breast-feeding? Insulin requirements usually fall during the first three months of pregnancy and increase for the remainder. If you are breast feeding, insulin and or diet may require adjustment.

•Is the patient a child under 12 years old?

Your insulin needs may also change if you drink alcohol.

You should also tell your doctor, pharmacist or diabetes nurse specialist if you are planning to go abroad. The time difference between countries may mean that you have to have your injections and meals at different times from when you are at home.

Using Humalog[®] Dosage

- You should normally inject Humalog[®] within 15 minutes before a meal. But your doctor will have told you exactly how much to use, when to use it, and how often. These instructions are only for you. Follow them exactly and visit your diabetes clinic regularly.
- If you change the type of insulin you use (for example from a human or animal insulin to Humalog[®]), you may have to take more or less than before. This might just be for the first injection or it may be a gradual change over several weeks or months.
- Inject Humalog[®] under the skin. You should only inject it into a muscle if your doctor has told you to.

Please read the back of this leaflet

What you should know about Humalog[®] in cartridges

Preparing Humalog[®]

- Humalog[®] is already dissolved in water, so you do not need to mix it. But you must use it **only** if it looks like water. It must be clear, have no colour and no solid pieces in it. Check this before each injection.

Getting the pen ready to use

- First wash your hands. Disinfect the rubber membrane of the cartridge.
- **You must only use Humalog[®] cartridges in Becton Dickinson injection pens or Lilly Diapens.** Follow the instructions that come with the pen. Put the cartridge into the pen.
- You will set the dose to 1 or 2 units. Then hold the pen with the needle pointing up and tap the side of the pen so that any bubbles float to the top. With the pen still pointing up, press the injection button on the B-D pen or the clip on the Diapen. Do this until a drop of Humalog[®] comes out of the needle. There may still be some small air bubbles left in the pen. These are harmless, but if the air bubble is too big, it may make the dose of your injection less accurate.

Injecting Humalog[®]

Clean your skin well where you are going to make the injection. Inject under the skin, as you were taught. Do not inject directly into a vein. Do not rub the area you have just injected. Make sure you inject at least half an inch (1cm) from the last injection and that you 'rotate' the places you inject, as you have been taught.

After injecting

As soon as you have had the injection, take the needle off the pen. This will keep the Humalog[®] sterile and prevent leaking. It will also stop air going back into the pen and the needle clogging up.
Do not share your needles.

Further injections

Leave the cartridge in the pen. Before every injection, dial 1 or 2 units and press the button or clip with the pen pointing up until a drop of Humalog[®] comes out of the needle. With the Becton Dickinson pen, stop using the cartridge if the leading edge of the plunger has gone as far as or beyond the coloured band. You can see how much Humalog[®] is left by looking at the gauge on the side of the cartridge. The distance between each mark on the gauge is about 10 units. With the Diapen, check to see if the blue part of the piston rod can be seen in the window. If it can the level it has reached on the scale shows how much insulin is left in the cartridge. If there is not enough for your dose, change the cartridge.

Do not mix any other insulin in a Humalog[®] cartridge. Once the cartridge is empty, do not use it again.

•**Emergencies and overdoses:** If your blood sugar is low, eat glucose tablets or sugar followed by fruit or biscuits, and then rest. This will often get you over a mild ‘hypo’ or minor insulin overdose. If you get worse and your breathing is shallow and your skin gets pale, tell your doctor at once. A glucagon injection can treat quite severe hypoglycaemia. Eat glucose or sugar after the glucagon injection. If you do not respond to glucagon, you will have to be treated in hospital. Ask your doctor to tell you about glucagon.

If ‘hypos’ or ‘hypers’ (see A and B) are not treated they can be very serious and cause headaches, nausea, vomiting, dehydration, unconsciousness, coma or even death.

- Always keep spare syringes and a spare bottle of Humalog[®], or a spare pen and cartridges, in case you lose your pen or cartridges or they get damaged.
- Always carry something to show you are diabetic.
- Always carry sugar with you.

While using your insulin

Common problems of diabetes

A. Hypoglycaemia

Hypoglycaemia (‘hypo’ - low blood sugar) means there is not enough sugar in the blood. This can be caused if:

- you take too much Humalog[®] or other insulin;
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- there is a change in your need for insulin; or

- you have trouble with your kidney or liver which gets worse.

Alcohol and some medicines can affect your blood sugar levels.

First symptoms of low blood sugar usually come on quickly and include:

- tiredness
- rapid heartbeat
- nervousness or shakiness
- nausea
- headache
- cold sweat.

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F. Date this leaflet was written

