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 3, 35396, Giessen, Germany or Lilly France S.A.,Rue du Colonel Lilly, 67640 Fegersheim, France.

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 that 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

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 H_2O, 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 France S.A.,Rue du Colonel Lilly, 67640 Fegersheim, France or 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.

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F.Date this leaflet was written

For more information, please contact the representative of Eli Lilly in your country:

Tiedotus Suomessa: Oy Eli Lilly Finland Ab, PL 16, 01641 Vantaa. Puh: 90-85 45 250.
Information lämnas i Finland av: Oy Eli Lilly Finland Ab, Box 16, 01641 Vanda. Tel: 90-85 45 250.

Information lämnas i Sverige av: Eli Lilly Sweden AB, Box 30037, 10425 Stockholm. Tel: (0)8 6199450.

Indirizzo per le comunicazioni in Italia: Eli Lilly Italia Spa, Via Gramsci 731/733, 50019 Sesto Fiorentino (FI). Tel: (0)55 42571

Kontaktadresse in Österreich: Eli Lilly Ges. m.b.H., Barichgasse 40-42, A-1030 Wien. Tel: 711 78-0.

Kontaktadresse in Deutschland: Lilly Deutschland GmbH, Niederlassung in 61343 Bad Homburg. Tel: 06172 273 426 Fax: 06172 273 230

Dirección de contacto en España: Lilly, S.A. , Avda. de la Industria 30, Poligono Industrial de Alcobendas, Alcobendas, 28100 Madrid. Tel: (1) 663 50 00.

Pessoas a contactar em Portugal: Lilly Farma, Produtos Farmacêuticos, Lda, Rua Dr. António Loureiro Borges, 4-Piso 3, Arquiparque- Miraflores, 1495 Algés. Tel: (1) 410 9595

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Kontakt in België. Contact en Belgique. Kontakt in Belgien: Eli Lilly Benelux n.v. -a.g., Rue de l’Etuve 52/1, Stoofstraat, Bruxelles 1000 Brussel. Tel: (02) 548 84 84.

Kontakt i Danmark: Eli Lilly Danmark A/S, Thoravej 4, 2400 København NV. Tlf: 38 16 86 00.

Pour toute information contacter en France: Lilly France, 203 Bureaux de la Colline, 92213 Saint-Cloud. Tel: (1) 49 11 34 34

For information in Ireland and the UK: Eli Lilly and Co. Ltd, Dextra Court, Chapel Hill, Basingstoke, Hampshire, RG21 5SY. Tel: (0)1256 315000

Informatie in Nederland: Eli Lilly Nederland BV, Krijtwal 17-23, 3432 ZT, Nieuwegein, Nederland. Tel: 030 60 25 800