SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Liprolog. For information on changes after approval please refer to module 8.

1. Introduction

Liprolog (insulin lispro) is an analogue protein of human insulin obtained by recombinant DNA technology which have a reverse position of the aminoacids at positions 28 (lysine) and 29 (proline) on insulin's B chain when compared to the natural sequence of the human insulin. This recombinant protein is synthesised in a special non-disease-producing laboratory strain of Escherichia coli bacteria that has been genetically modified and subsequently transformed and purified in a series of steps to yield zinc-insulin lispro crystals which are then formulated into the final drug product.

The main disadvantages associated with the regular marketed insulin preparations in controlling the post-prandial glucose levels, a slow onset effect and a long-lasting hypoglycemic activity, can be minimised by the administration of insulin lispro. Thus, after insulin lispro subcutaneous administration a faster absorption from the administration site with a more rapid onset and shorter duration of hypoglycemic action has been observed when compared to regular insulin.

The application contains appropriate pharmaceutical data as well as pre-clinical and clinical information to meet the quality, safety and efficacy standards.

2. Chemical, pharmaceutical and biological aspects

Liprolog, insulin lispro, is an analogue of human insulin of recombinant DNA origin. Insulin lispro is identical to human insulin in terms of its primary aminoacid sequence except for an inversion of the natural proline-lysine sequence on the B-chain at positions 28 and 29. The compound was selected as a rapid acting insulin based on its physicochemical characteristic of weak self-association in solution and on its monomeric properties.

Insulin lispro is supplied either as a clear, colorless solution or as a suspension for parenteral administration.

Insulin lispro is produced from a protein that is expressed by a gene incorporated into a plasmid. The plasmid is contained within the K-12 strain of *Escherichia coli*. Material extracted from *E coli* is processed and purified at different steps by appropriate chromatographic extraction.

Appropriate methods are implemented to ensure microbiological control during the different steps of insulin lispro processing.

Several methods of characterising the aminoacid sequencing of insulin lispro, such us peptide mapping and X-ray crystallography has been satisfactory utilised.

The supporting data on process validation include the removal of impurities during the purification process. The levels of materials such as tetracycline, host cell proteins, endotoxins, enzymes used in conversion and process intermediates have been considered in the drug substance or at points during down stream processing. The related substances arising from degradation have also been adequately investigated.

The rationale of using m-Cresol as a preservative and a stabiliser agent has been properly justified and documented. Other excipients include tonicity modifier (glycerol), buffering agent (dibasic sodium phosphate), stabiliser (zinc oxide) and pH adjustment for the vehicle.

The shelf life of the product is 24 months if stored between 2 and 8 ºC.

The Company has completed a declaration of compliance with annex to Directive 75/318/EEC, as amended by Directive 1999/82/EEC relating to TSE.

Disposable Pens

Liprolog-Pen: the Pen contains a non-reusable 3.0 ml (100 U/ml) Liprolog cartridge that is permanently sealed inside the device. It delivers up to 60 units per dose in increments of 1 unit.

3. Toxico-pharmacological aspects

The Marketing Authorisation Holder of Humalog, Eli Lilly Nederland B.V., consented to the clinical data contained in the original files for Humalog being used for the purpose of examining this application.

Pharmacodynamics

The total glucodynamic effects of insulin lispro were indistinguishable from human insulin after subcutaneous administration in rats, dogs, rabbits and pigs. A reduction of 50% on the glucose measurements has been found after administering subcutaneous doses in different animal species.

Insulin lispro is biologically equivalent to insulin in several in vitro tests including insulin receptor binding in cultured lymphocytes, human placenta and human liver, and glucose transport in adipocytes. Aspartate B10 insulin shown about a 4-5 fold higher binding affinity for the IGF-1 receptor.

In cell growth assays using human smooth muscle cells and human mammary epithelial cells and using [^{3}H] thymidine incorporation or increases in cell number as an index of cell growth, insulin lispro was shown to be equipotent to human insulin. AspB10 insulin was about 3-fold more potent than human insulin and insulin lispro in mammary epithelial cells and in one of the two experiments using smooth muscle cells it was 14 times more potent than insulin.

Studies intended to investigate potential secondary pharmacological effects revealed no unexpected effects, and changes on the EEG recording which were found in a cardiovascular experimental study carried out in anaesthetised dogs were considered to be due to the hypoglycaemia.

Pharmacokinetics

The pharmacokinetic profile was developed in rats and dogs and included pharmacokinetics, tissue distribution and elimination studies.

Toxicology

No clinical signs or other effects were observed in the single toxicity studies that have been conducted in rats and in dogs by the intravascular and subcutaneous route of administration.

Repeated toxicity studies of 1 month, 6 and 12 months duration in rats and of 1 month and 12 months duration in dogs were conducted after subcutaneous administration. No unexpected findings were seen in any of these studies.

There was no evidence of inducing neutralising antibodies in 1 month and 12 months studies with dogs.

There was no evidence of mutagenic potential in a battery of mutagenicity studies as recommended by the CPMP guidelines and conducted according to the GLP and contemporary standards.

No evidence of a tumourigenic effect was seen in a 12- month study in Fischer 344 rats. Such a finding, however, was observed in another 12- month toxicological study carried out with Sprague-Dawley rats at similar doses of a different insulin analogue (Aspartate B10 insulin). Carcinogenic studies have not been conducted with insulin lispro. With the absence of mutagenic or clastogenic effects and no proliferative effect in chronic one year toxicity studies the experts consider that there is no need to conduct rodent carcinogenicity bioassays on the basis of the overall toxicological information currently available. Moreover, the company was requested to submit new additional ‘in vitro cell’ studies to assess the stimulation on DNA synthesis of insulin lispro compared to human insulin and Aspartate B 10 insulin in Hep G2 human hepatoma cells by measuring incorporation of BrdU and [3H]-thymidine. The overall results of all replicates did not demonstrate any mitogenic properties.

As far as the reproductive toxicity information is concerned, a combined fertility, embryotoxicity, perinatal and postnatal study was carried out in female and male rats treated during the two weeks prior to mating and the mated females were treated throughout gestation and lactation. The fertility of male rats was also assessed during the 6-month chronic toxicity study following 5 months of treatment with insulin lispro. And finally an embryo-foetal toxicity study was conducted in rabbits. The overall results show that there are no relevant adverse reproductive effects in the animal studies which could cause any concern to the prescribing physician.

4. Clinical aspects

The Marketing Authorisation Holder of Humalog, Eli Lilly Nederland B.V., consented to the clinical data contained in the original files for Humalog being used for the purpose of examining this application.

Pharmacodynamics and pharmacokinetics properties

The pharmacodynamic and pharmacokinetic studies were carried out in three randomised crossover open studies in normal volunteers using the clamp method and biostator to keep the glucose blood level as close to fasting as possible. Insulin lispro was compared to regular soluble human insulin (Humulin R). The absolute bioavailability after subcutaneous administration compared to the intravenous route has been studied. Insulin lispro also displays a linear kinetic behaviour up to dose of 0.2 U/kg. A consistent pattern of kinetics with a shorter T_{max} and half-life and with a higher C_{max} was observed for insulin lispro when compared to the comparative insulin preparation. A higher glucose infusion early after insulin lispro dosing was required but a lower total glucose was infused.

No kinetic changes were observed when insulin Ultralente was given mixed together or at separate sites with insulin lispro. A small decrease in C_{max} and a slight increase in T_{max} values were the only changes observed in the kinetics of insulin lispro when mixed in the same syringe with human isophane insulin**.**

Data obtained from one study performed in healthy volunteers suggest that there are no differences between insulin lispro and the comparator on the counter regulatory hormone responses to hypoglycaemia measured as GH, adrenaline, nor-adrenaline, cortisol and symptoms.

Some additional pharmacokinetic information was obtained from three studies involving diabetic patients. A great inter- and intra-varibility was observed for both insulin treatments. In line with the results previously obtained with normal subjects, the insulin lispro showed an earlier and a higher peak with a similar AUC, and showed less intra-subject variability.

It is well known that the liver clears the insulin and the most non-hepatic clearance is by the renal route. Previous studies have shown that the insulin kinetics are altered by the renal impairment associated with diabetes. There was no difference between the two insulins in insulin clearance in renally impaired patients. This study showed that only slightly higher levels were observed in anephric patients. Nonetheless, this population could not be extrapolated to the diabetic subgroup of patients with associated renal dysfunction.

Clinical efficacy

The efficacy of this new modified recombinant human insulin preparation has been studied in eight clinical trials involving 2951 diabetic patients who were randomised to the experimental insulin lispro treatment or to Humulin R (Lilly soluble rDNA human insulin).

In all studies one or two daily doses of long-acting insulin (NPH or Ultralente) were combined with the short acting insulin before each meal. While there were no clinical therapy studies carried out by using the intravascular route, pharmacokinetic studies demonstrated no differences in the activity of insulin lispro compared to human insulin when given intravenously.

As major differences exist between the kinetic behaviour of insulin lispro compared to the regular insulin, an open design was considered to be more appropriate rather than using a double-blind one. Thus, the Humulin R should be given 30-45 minutes before a meal and the investigational insulin should be injected immediately. The double dummy technique was not used since it was felt that

patients would not comply with two injections before each meal over a one year period. Nonetheless, it has been recognised that many patients do inject the regular insulin just before a meal without keeping the recommended preprandial optimal time.

The criteria to define the population to be enrolled into the studies were very similar and four of them included Type I and the other four Type II diabetes. Six studies were one year parallel group comparisons; of these, two were carried out in new diabetics and four in established diabetics; the comparator was insulin ultralente in two studies and under NPH insulin in the other four studies. The remaining two studies were performed following a crossover design keeping each insulin for a three months duration. A summarised description of the main features of the therapeutic clinical studies is shown in table 1.

Table 1: Main features of the therapeutic clinical trials

STUDY CODE	**No. OF PATIENTS** Randomisd Completed I-Lispro	**AGE /MEAN years (%Fem/Male)**	**TYPE OF DIABETES**	**BASAL INSULIN**	**DURATION months** (average)	**STUDY DESIGN**	**DURATION OF DIABETES years** (mean)
IOAA	167 153 81	30.7 (52.6/47.4)	Type I	Humulin Zn[a]	12	A	12.8
IOAB	145 141 72	56.5 (48.7/51.32)	Type II	Humulin Zn[a]	12	A	11.6
IOAC	169 169 81	33.7 (48.3/51.7)	Type I	Humulin I[b]	12	A	11.8
IOAD	150 139 73	55.5 (50.6/49.4)	Type II	Humulin I[b]	12	A	12.7
IOAE	98 88 50	24.4 (38.8/61.2)	Type I	New diabetic patients[c]	12	A	0.18
IOAF	375 317 186	59.06 (43.8/56.2)	Type II	New diabetic patients[c]	12	A	7.83

IOAG	1008 960[d]	33.42 (41.9/58.12)	Type I	Humulin Zn[a] Humulin I[b]	6	B	12.14
IOAH	722 684[d]	58.6 (45.4/54.1)	Type II	Humulin Zn[a] Humulin I[b]	6	B	12.55

[a)] Ultralente basal insulin
[b)] NPH insulin
[c)] Treated with insulin preparation for < 2 months
[d)] Patients who completed both treatments periods

[A)] Randomised parallel controlled open-label design
[B)] Randomised cross-over open-label design

All trials investigated the same primary variables (HbA_{1c}, fasting glucose and post-prandial control at 1 and 2 hr for blood glucose and glucose excursions), and numerous secondary variables (% patients with 2 hr post-prandial glucose less than 8 mmol/L, % patients with 2 hr post-prandial glucose within 20% of fasting, % patients with a 50% decline from baseline in 2 hr post-prandial glucose, % patients with at least one of the above, incidence and rate of hypoglycaemia, total and basal insulin dose, weight and lipid levels). All of the studies were well conducted and followed Good Clinical Practice recommendations.

The overall results of the pivotal studies are summarised in table 2.

Table 2: Main therapeutic outcome of the clinical studies

Variable values expressed as mean on therapy, in each box the value above refers with Insulin lispro and the one below with the corresponding for Humulin R

	HbA_{1c} (%)	**Postprandial Glucose (mmol/L)**		**Postprandial Excursions (mmol/L)**		**Secondary Variables**
		1st hour	**2nd hour**	**1st hour**	**2nd hour**	
IOAA	trend to lower levels lispro[a]	11.63[b] 13.53	11.32[ab] 13.29	1.50[a] 3.25	0.07[a] 2.92	not relevant
IOAB	nsd[c]	11.44[b] 13.22[b]	11.41[b] 12.69[b]	2.07[ab] 3.01[b]	1.04[ab] 2.49	2 hour postprandial glucose ≤ 8 mmol/L[d]
IOAC	nsd[c]	14.05 13.52[b]	13.06 12.76	3.01 3.63	1.99 2.75	not relevant

IOAD	nsd[c]	1 3.72[b] 1 3.75[b]	12 .32[b] 13 .19[b]	3.12 3.39	1.74[a] 2.84	not relevant
IOAE	nsd[c]	1 2.73 1 3.14	11 .44 12 .39	2.59 3.53	1.31 2.78	not relevant
IOAF	nsd[c]	1 3.28 1 3.49	12 .31 12 .95	3.37 3.38	2.38 2.83	not relevant
IOAG	nsd[c]	1 2.91[a] 1 3.89	11 .16[a] 12 .87	1.24[a] 2.53	- 0.51[a] 1.52	2 hour postprandial glucose ≤ 8 mmol/L[e]
IOAH	nsd[c]	1 3.23[a] 1 3.89	12 .08[a] 13 .14	2.59[a] 3.74	1.40[a] 2.97	2 hour postprandial glucose ≤ 8 mmol/L[f]

[a] $p < 0.05$ insulin lispro compared with Humulin R
[b] $p < 0.05$ compared with baseline of each treatment
[c] nsd: no significant differences between groups
[d] 33.3% for insulin lispro vs 13.9% Humulin ($p < 0.05$)
[e] 31.3% for insulin lispro vs 23.4% Humulin ($p < 0.05$)
[f] 19.6% for insulin lispro vs 12.1% Humulin ($p < 0.05$)

There were no statistical differences in all studies between both treatment groups on the indices of diabetic control based on the HbA_{1C} and the fasting glucose levels. Haemoglobin A_{1c} at endpoint was significantly lower in one study (IOAA) for insulin lispro but the observed differences are too small and less than the differences between groups at baseline. The post-prandial diabetic control was investigated by giving the usual standard breakfast after an overnight fast. In most studies the glucose levels were significantly lower on insulin lispro but this difference was not always significant. Both of the crossover studies (IOAG and IOAH) showed a significant advantage for insulin lispro in one and at two hours glucose levels and excursions. The long-term studies indicated that levels decreased in the first month in both treatment arms but tended to increase again over the later part of the study. The glucose excursions at one hour and at two hours were lower with insulin lispro although statistical differences were not achieved in 4/8 studies at one hour and in 2/8 studies for the 2-hour levels. The incidence of hypoglycaemias was similar in both groups, however the rate of hypoglycaemia was lower in the insulin lispro groups, especially in the Type I patients. No effect on weight, lipid levels and dose of insulin were found.

Although an attempt was made to quantify the impact on the quality of life the open-label design as well as the complex questionnaire used precluded concise conclusions. The results obtained from patient preference measurements indicated that patients preferred to remain on therapy with insulin lispro at the conclusion of studies IOAA and IOAH.

Two clinical trials (IOCF, IOBJ) were performed in order to support the indication *Use in children below 12 years of age*. IOCF study involved 60 children aged 2.9 to 11.4 years in which three therapeutic strategies were compared (insulin lispro before meals, insulin lispro after meals, Humulin R before meals): efficacy in controlling glucose profile in prepubertal children with Type I diabetes and safety were monitored. IOBJ study involved 463 adolescents aged 9-18 years: the primary objective was to compare insulin lispro to Humulin R with respect to glucose excursion in adolescents

with Type I diabetes. Efficacy and safety data from these trials did not present any cause for concern and the approval for this indication has been granted.

Insulin lispro has been granted approval for occasional postprandial administration, following evaluation of the data from two clinical trials: IODQ compared administration of insulin lispro 20, 0 minutes before or 15 minutes after a meal with standard administration regimens of Humulin R (40 - 20 - 0 minutes before a meal); IOCF study has been described previously (see indication for administration to children).

Clinical safety

The evaluation of the clinical safety entails 2247 patients who were exposed to the insulin lispro and 2265 patients who received Humulin R. About 311 (13.6%) of the patients were treated with insulin lispro for one-year period and 961 (42.2%) were under treatment for 6 to 12 months.

Five patients died under insulin lispro treatment and 7 under Humulin R. The majority of deaths were caused by myocardical infarction and cardiovascular related conditions (4 for insulin lispro and 3 for Humulin R), cancer (2 for Humulin R and 1 for insulin lispro), hyperglycaemia and severe ketosis (both for Humulin R). None of these deaths seemed to be related to the insulin type.

The withdrawal rate from the studies was very low. Twenty patients on each treatment arm withdrew due to adverse events. Of them, 11 were unintended pregnancy and most of the remainder were due to intercurrent illness. One patient on Humulin R was withdrawn because of insulin allergy.

There were 15 serious or unexpected events reported. Five on Humulin and 10 on insulin lispro. Many of these were cardiovascular events or hyperglycaemia, and were usually associated with infection.

The most common adverse events were headache, pharyngitis, rhinitis, flu and infection. There were no differences between both treatment groups. Of the treatment-emergent adverse events the hyperglycaemia appeared to be higher on insulin lispro (37 episodes) rather than on the Humulin R treatment (22 episodes). This adverse event occurred in the early stages of the study and it has been attributed to the shorter duration of the action of the insulin lispro.

Adverse events in the elderly population had a higher incidence of urinary tract infections for Humulin R (5.8%) compared to insulin lispro (1.8 %). Hyperglycaemia was reported in 1.5% of patients in each group.

The hypoglycaemic episodes were analysed in a comprehensive manner sorting out the symptomatic and asymptomatic (blood sugar below 3.5 mmol/L) in the same group. Eighteen serious hypoglycemic episodes were reported (17 in Type I patients). Three of the 18 events were associated with hypoglycemic comas and occurred in Type I patients treated with Humulin R. The rate (episodes/30 days) of hypoglycaemia was significantly reduced in Type I patients on insulin lispro. Reduction of hypoglycaemia in Type II patients receiving insulin lispro did not achieve statistical significance in all studies.

Most patients were able to self-treat over 95% of the hypoglycaemic episodes. Less than 1% required glucagon or iv glucose administration and there were no difference between groups o when compared each group with the corresponding baseline period. No differences between groups were seen in those patients who reported coma (less than 1%).

Additional information on safety using insulin lispro has been obtained from the open 1 year extension of the four parallel studies. This on-going study involves 272 patients and at the 4-months follow-up no differences in the pattern of the adverse events have been observed. Another similar study involves 680 patients who will be followed during 1-year extension after they completed the crossover trials. Data at 4 months are available and there are no differences in the pattern of the adverse events reported.

No clinically relevant immunogenicity has been found on the intensive monitoring of the immune response in the clinical trials. Specific antibodies increased slightly in both groups from baseline but no differences were found between them.

Following the assessment of the first PSUR, although no increased risk of hypoglycaemia seemed associated to insulin lispro compared to other insulins, a driving warning and warning about the risks

of hypo- and hyperglicaemia are being included in the SPC and PIL in order to harmonise the product information with other centrally authorised insulins on the market.

Mixes

Four pharmacokinetic and three clinical studies are included in the application. The pharmacokinetic studies have established the time course of activity of Humalog NPL, Mix 25 and Mix50, and the clinical studies have demonstrated acceptable efficacy and safety.

Pharmacokinetics

Four pharmacokinetic studies are presented in the application:

A study in healthy volunteers comparing single injections of insulin NPL with single injections of insulin NPH, two studies in healthy volunteers comparing the effects on single injections of five different mixing ratios of insulin lispro and insulin NPL and a two way cross-over study comparing insulin NPL with insulin NPH for overnight glucose control in patients with Type 1 diabetes.

Pharmacokinetics of intermediate-acting formulation of insulin lispro

In this non-blinded randomised, two-way crossover single dose comparison of insulin NPL (Humalog NPL insulin) with insulin NPH (Humulin N insulin), eight healthy volunteers, aged 19-36 years, received a 0.4 U/kg dose of each insulin, separated by at least 7 days. Blood glucose was measured approximately every 5 minutes, and glucose was infused to maintain constant blood glucose concentrations similar to fasting glucose levels for 15 hours while samples were collected for assay of insulin lispro/insulin. The volunteers remained fasting and resting in bed.

Mean glucose infusion rate versus time curves showed a greater infusion rate was required for the first 6 to 7 hours after injection for NPL than for NPH. After 7 hours the glucose infusion requirements were nearly identical.

The peak concentrations and hypoglycaemic activities of the two intermediate acting insulins appeared similar, with a possible earlier peak of activity for insulin lispro.

Pharmacokinetics of free mixtures of insulin lispro and insulin lispro protamine

In this non-blinded randomised crossover single dose comparison of extemporaneously prepared mixtures of insulin lispro (Humalog) and NPL (Humalog NPL), ten healthy volunteers, aged 21-30 years, received a 0.3 U/kg dose of one of the mixtures of insulinon occasions separated by at least 5 days. Blood glucose was measured approximately every 5 minutes, and glucose was infused to maintain constant blood glucose concentrations similar to fasting glucose levels for 20 hours, or until no further glucose was required if earlier, while samples were collected for assay of insulin lispro/insulin. The volunteers remained fasting and resting in bed.

As expected, mean glucose infusion rate versus time curves showed a greater maximum infusion ratewith increase in the proportion of insulin lispro.

Maximum serum concentration rises with the proportion of insulin lispro in the mixture.

Pharmacokinetics of insulin lispro premixtures: a comparison of insulin lispro, low mixture, mid mixture, high mixture and insulin lispro protamine suspension

In this non-blinded randomised crossover single dose comparison of manufactured mixtures of insulin lispro (Humalog) and insulin NPL (Humalog NPL), 31 healthy volunteers, aged 22-33 years, received a 0.3 U/kg dose of each of the mixtures of insulin, NPL alone and insulin lispro alone on five occasions separated by at least 7 days. Blood glucose was measured approximately every 15 minutes, and glucose was infused to maintain constant blood glucose concentrations similar to fasting glucose levels for 22 hours, or for 10 hours for the unmixed insulin lispro, while samples were collected for assay of insulin lispro/insulin. The volunteers remained fasting and resting in bed.

As expected, mean glucose infusion rate versus time curves showed a greater maximum infusion rate, with increase in the proportion of insulin lispro.

Maximum serum concentration rises, with the proportion of insulin lispro in the mixture.

Overnight glycaemic control following evening administration of insulin lispro protamine suspension (NPL): Comparison with evening administration of human NPH in patients with Type 1 diabetes

In this randomised double-blind crossover comparison, 12 patients aged 19 to 48 years, whose Type 1 diabetes was well controlled using a short-acting insulin before meals and human NPH at bedtime, used insulin lispro as their pre-dinner short-acting insulin, and received on the first occasion either insulin NPL or insulin NPH at 2200 at a dose previously established for insulin NPH. Dextrose infusion was given as necessary to maintain the blood glucose level above 3.5 mmol/L. At 0900 hours a single dose of insulin lispro was given before breakfast and monitoring was continued until 1100 hours. On the second occasion each patient repeated the procedure with the alternative intermediate acting insulin.

Curves for blood glucose infusion rates, blood glucose and free serum insulin levels were almost superimposable, suggesting that the absorption profiles of the two intermediate acting insulins are very similar and are equally effective as bedtime insulins.

Efficacy

Three clinical studies are presented in the application:

- a randomised parallel study in adults, comparing glucose control using free mixtures, between Humalog (insulin lispro) with Humalog NPL and Humulin N with Humulin R
- a randomised cross-over study in adults, comparing glucose control using fixed mixtures of Humalog Mix25 (25% lispro 75% NPL) and Humulin 20/80
- a randomised cross-over study in adults, comparing glucose control between a Humalog fixed mixture (75% lispro, 25% NPL) and standard Humulin R

Free mixtures of insulin lispro protamine suspension (NPL) and insulin lispro: comparison with free mixtures of Humulin N and Humulin R in a twice daily regimen in the treatment of diabetes

This was a multicentre, multinational study. 166 patients, 112 male and 54 female, age 18 to 75 years, were randomised in the study. 102 had insulin-dependent diabetes and 64 had non-insulin-dependent diabetes; all were receiving insulin at the time of entry to the study.

Patients were randomised to receive twice a day (before the first and evening meals) in a self-mix combination **either** insulin lispro and insulin NPL **or** human insulin and insulin NPH. Treatment with the assigned combination continued for 6 months. The investigator adjusted dosage. Control was assessed by haemoglobin A_{1C} levels, eight point blood glucose profiles and number of hypoglycaemic episodes, compared with values for a baseline period prior to randomisation.

After six months the two regimes appeared broadly similar, in terms of both dose and glucose control.

Twice daily treatment with insulin lispro low mixture: a comparison with premixed human insulin 20/80

This was a multicentre, multinational cross-over study. 127 patients, 59 male and 68 female, were randomised in the study. 75 had insulin-dependent diabetes and 52 had non-insulin-dependent diabetes; all were receiving insulin at the time of entry to the study.

Patients were randomised to receive twice a day (before the first and evening meals) in premixed combination **either** 25% insulin lispro 75% insulin NPL (Humalog Mix25) given immediately before meals **or** 20% human insulin 80% insulin NPH (Humulin 20/80) given 30-45 minutes before the meal. Treatment with the assigned combination was to continue for 3 months, after which patients changed to the alternative regime. The investigator adjusted dosage. Control was assessed by haemoglobin A_{1C} levels, eight point blood glucose profiles and number of hypoglycaemic episodes, compared with values for a baseline period prior to randomisation.

The two regimes appeared broadly similar, in terms of both dose and glucose control. The clinical data and expert report support the clinical utility of this formulation.

Insulin Lispro Mid Mixture and Insulin Lispro Low Mixture: Comparison with Human Insulin 50/50 and Human Insulin 30/70 given twice daily in the treatment of diabetes

This was an open-label, 6 month cross-over study comparing morning administration of Humalog Mix50 with standard Human Insulin 50/50 , and evening administration of Humalog Mix25 with Human Insulin 30/70. Two ratios were used in this study because a higher dose of soluble insulin is often considered necessary before breakfast than before dinner. Study end points related to glucose control as judged by haemoglobin A1C, self-monitored glucose profiles, and frequency of self-reported hypoglycaemia.

A total of 100 patients aged 18 - 70 participated in the study. Of these, 37 were judged to have type 1 diabetes mellitus and 63 type 2 diabetes. Each individual was treated for 3 months with each insulin.

The two regimes appeared broadly similar, in terms of both dose and glucose control. The clinical data and expert report support the clinical utility of this formulation.

Summary and conclusions on efficacy

The requested indication is as follows:

Humalog NPL (Mix25, Mix50) is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

The clinical studies submitted support the requested indication for all formulations.

Safety

No deaths or serious adverse events were reported during these studies in healthy volunteers. One moderately severe episode of asthma occurred in a patient with a previous history of asthma. The other adverse events reported were those to be expected in volunteer studies of this nature, with no imbalance between treatments. In the clinical studies, one death was reported (suicide) and 41 randomised patients reported at least 1 serious adverse event. There were no unexpected serious adverse events possibly related to the study drug

Serious adverse events related to the treatment were:

- accidental overdoses
- hospitalisations due to hyperglycaemia and
- hospitalisation due to hypoglycaemia

These events are not uncommon in patients with diabetes using insulin.

There was no significant difference between groups concerning incidence and characteristics of hypoglycaemic episodes. Routine clinical laboratory tests showed no clinically significant differences between the groups. Assessment of insulin lispro specific human insulin specific and cross reactive antibodies provided no grounds for concern.

Conclusion

Liprolog insulin lispro is an analog of human insulin. It is created when the amino acids at positions 28 and 29 on insulin's B chain are reversed. At physiologic concentrations insulin lispro exists in solution as a monomer which allows a higher rate of absorption from the subcutaneous sites of injection in relation to regular human insulin.

Liprolog is synthesised in a special non-disease-producing laboratory strain of Escherichia coli bacteria that has been genetically modified and is subsequently transformed and purified in a series of steps to yield zinc-insulin lispro crystals. These crystals are then formulated into the final drug product. The potential for viral contamination due to material of biological origin and the removal of impurities during all main processing steps have been adequately assessed.

The pharmacodynamic effects of insulin lispro on blood glucose control and on binding both insulin and IGF-1 receptors have been adequately assessed. No relevant findings have been observed during the toxicity studies after single dose and at 1 month and 12 months repeated administration. There was no evidence of effects on the fertility, development-toxicity and teratogenicity in the animal species studied. As the result of the mutagenic potential assessed through several series of tests was uniformly negative, and no proliferative effect has been observed, there was no need to conduct conventional carcinogenicity data.

Based on the overall clinical data submitted, the insulin lispro appears to display efficacy and safety profiles comparable to those of existing human insulin. Most studies demonstrate reduced post-prandial glucose elevations, despite an insulin lispro injection time just before meals. Two large studies with diabetic patients demonstrate a reduced rate of hypoglycaemia in insulin lispro treated patients, without worsening of metabolic control (HbA_{1c}).

Summary and conclusions on clinical safety (Mixes):

Adequate clinical data have been provided in order to demonstrate the safety of Liprolog Mix25 and Liprolog Mix50 for the approved indication.

5. Overall conclusions and benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Liprolog was favourable in the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis and for the initial stabilisation of diabetes mellitus.