

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 July 2004 For scientific information on procedures after this date please refer to module 8B.**

### 1. Introduction

Humalog (insulin lispro) is an analogue protein of human insulin obtained by recombinant DNA technology that 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

Humalog, 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 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 as peptide mapping and X-ray crystallography has been satisfactory utilised.

Some questions have been put to the company regarding the impurities arising from the expression system, fermentation and down stream processing and from degradation. A major question was raised because insulin lispro had not been produced at the commercial scale. The supporting data on process validation includes 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 °C.

#### Disposable Pens

Humalog-Humaject: HumaJect pen contains a non-reusable 3.0 ml (100 U/ml) Humalog cartridge which is permanently sealed inside the device. It delivers up to 96 units per dose in increments of 2 units.

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

### **3. Toxicopharmacological aspects**

#### **Pharmacology**

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 [<sup>3</sup>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**

##### **Pharmacodynamic and pharmacokinetic 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-variability 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 is 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 Randomised 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 <sup>a</sup>	12	A	12.8
IOAB	145 141 72	56.5 (48.7/51.32)	Type II	Humulin Zn <sup>a</sup>	12	A	11.6
IOAC	169 169 81	33.7 (48.3/51.7)	Type I	Humulin I <sup>b</sup>	12	A	11.8
IOAD	150 139 73	55.5 (50.6/49.4)	Type II	Humulin I <sup>b</sup>	12	A	12.7
IOAE	98 88 50	24.4 (38.8/61.2)	Type I	New diabetic patients <sup>c</sup>	12	A	0.18
IOAF	375 317 186	59.06 (43.8/56.2)	Type II	New diabetic patients <sup>c</sup>	12	A	7.83
IOAG	1008 960 <sup>d</sup>	33.42 (41.9/58.12)	Type I	Humulin Zn <sup>a</sup> Humulin I <sup>b</sup>	6	B	12.14
IOAH	722 684 <sup>d</sup>	58.6 (45.4/54.1)	Type II	Humulin Zn <sup>a</sup> Humulin I <sup>b</sup>	6	B	12.55

a) Ultralente basal insulin

A) Randomised parallel controlled open-label design

b) NPH insulin

B) Randomised cross-over open-label design

c) Treated with insulin preparation for  $\leq 2$  months

d) Patients who completed both treatments periods

All trials investigated the same primary variables (HbA<sub>1c</sub>, 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 <sub>1c</sub> (%)	Postprandial Glucose (mmol/L)		Postprandial Excursions (mmol/L)		Secondary Variables
		1st hour	2nd hour	1st hour	2nd hour	
<b>IOAA</b>	trend to lower levels lispro <sup>a</sup>	12.63 b 13.53	11.32 <sup>a</sup> b 13.29	1.50 <sup>a</sup> 3.25	0.07 <sup>a</sup> 2.92	not relevant
<b>IOAB</b>	nsd <sup>c</sup>	12.44 b 13.22 b	11.41 <sup>b</sup> 12.69 <sup>b</sup>	2.07 <sup>a</sup> b 3.01 b	1.04 <sup>a</sup> b 2.49	2 hour postprandial glucose ≤ 8 mmol/L <sup>d</sup>
<b>IOAC</b>	nsd <sup>c</sup>	14.05 13.52 b	13.06 12.76	3.01 3.63	1.99 2.75	not relevant
<b>IOAD</b>	nsd <sup>c</sup>	13.72 b 13.75 b	12.32 <sup>b</sup> 13.19 <sup>b</sup>	3.12 3.39	1.74 <sup>a</sup> 2.84	not relevant
<b>IOAE</b>	nsd <sup>c</sup>	12.73 13.14	11.44 12.39	2.59 3.53	1.31 2.78	not relevant
<b>IOAF</b>	nsd <sup>c</sup>	13.28 13.49	12.31 12.95	3.37 3.38	2.38 2.83	not relevant
<b>IOAG</b>	nsd <sup>c</sup>	12.91 a 13.89	11.16 <sup>a</sup> 12.87	1.24 <sup>a</sup> 2.53	- 0.51 <sup>a</sup> 1.52	2 hour postprandial glucose ≤ 8 mmol/L <sup>e</sup>
<b>IOAH</b>	nsd <sup>c</sup>	13.23 a 13.89	12.08 <sup>a</sup> 13.14	2.59 <sup>a</sup> 3.74	1.40 <sup>a</sup> 2.97	2 hour postprandial glucose ≤ 8 mmol/L <sup>f</sup>

<sup>a</sup> p < 0.05 insulin lispro compared with Humulin R

<sup>b</sup> p < 0.05 compared with baseline of each treatment

<sup>c</sup> nsd: no significant differences between groups

<sup>d</sup> 33.3% for insulin lispro vs 13.9% Humulin (p < 0.05)

<sup>e</sup> 31.3% for insulin lispro vs 23.4% Humulin (p < 0.05)

<sup>f</sup> 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<sub>1c</sub> and the fasting glucose levels. Haemoglobin A<sub>1c</sub> 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 myocardial 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 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 hyperglycaemia are being included in the SPC and PIL in order to harmonise the product information with other centrally authorised insulins on the market.

### *Conclusion*

Humalog 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.

Humalog 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<sub>1c</sub>).

Consequently, a favourable opinion for granting a marketing authorisation is recommended for the following 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 stabilisation of diabetes mellitus. Humalog is a short acting insulin and may be used in conjunction with a longer acting human insulin.

## **5. Post marketing experience**

### **Use in children**

New data on the use of insulin lispro in adolescents and children was presented. The efficacy and safety data from the clinical trials in children and adolescents did not present any cause for concern about the use of insulin lispro in these age groups. Clinical trials were performed in children (61 patients aged 2 to 11) and children and adolescents (481 patients aged 9 to 19 years), comparing insulin lispro to human soluble insulin. The pharmacodynamic profile of insulin lispro in children is

similar to that seen in adults. Sections 4.1, 4.4 and 5.1 of the SPC and relevant sections of the PL were updated to reflect this information.

#### **Information on postprandial dosing**

The MAH has submitted data about occasional postprandial injection of insulin lispro. The statement “when necessary Humalog can be given soon after meals” was added to Section 4.2 of the SPC.

#### **CE marked pen injection systems**

The instructions for use and handling of cartridges were updated with a statement specifying that 1.5 and 3.0 ml cartridges are to be used in conjunction with compatible CE marked pen injection systems.

#### **Warning on driving and operating machinery**

Following the evaluation of the first PSUR, the CPMP identified the need of an improvement in the driving and operating machinery warning in Humalog SPC and PL, harmonised with other centrally authorised insulins. The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia, and therefore, a warning on driving and operating machinery was inserted on Section 4.7 of the SPC and relevant section of the PL.

#### **Administration of Humalog with subcutaneous infusion pumps**

Section 4.2 and 6.6d of the SPC were updated with information on the administration of Humalog with subcutaneous infusion pumps. It was highlighted that only certain Minimed and Disetronic insulin infusion pumps may be used to infuse insulin lispro.

#### **Risk of ketoacidosis and hyperglycaemia**

Following a request from the CPMP, a warning was inserted in section 4.4 of the SPC, concerning the potential risk of ketoacidosis and hyperglycaemia in the event of an under dosage of insulin lispro.

#### **Update on renal and hepatic impairment**

Eli Lilly made a commitment to provide a final study report of Humalog pharmacokinetics in patients with renal and hepatic impairment. The assessment of the results of clinical trials with patients with renal/hepatic impairment demonstrated that the pharmacokinetics of Humalog and Humulin R were independent from renal function. Humalog maintained more rapid absorption and elimination when compared to Humulin R in patients with hepatic impairment.

Sections 4.4, 5.1 and 5.2 of the SPC were updated with this information.

#### **Additional route of administration (intravenous)**

The MAH submitted an application to include a new route of administration (intravenous use). Until that moment, the authorised route of administration for Humalog was subcutaneous use.

The Applicant submitted two studies to support the intravenous use of Humalog solution for injection (vial, cartridge and pen). The data submitted suggested that Humalog, given intravenously in circumstances as acute illness or during and after surgery, might be effective and safe in controlling hyperglycaemia in diabetic patients. Sections 4.2 and 6.6 of the SPC and the PL were updated with this information.

#### **Use of Humalog with sulphonylurea drugs**

Combination therapy with insulin and sulphonylurea drugs is often used in patients with type 2 diabetes. The MAH applied for a variation to update sections 4.2 and 5.1 of the SPC with current information regarding the use of Humalog with sulphonylurea drugs; providing data from two studies indicating that Humalog is effective and safe when combined with sulphonylurea agents. Both sections of the SPC were updated.

#### **The effect of various injection sites on insulin absorption**

The MAH provided the results of a pharmacodynamic study where insulin lispro showed a greater maximum infusion rate, at an earlier time regardless of the injection site (deltoid, femoral or abdominal) compared to soluble human insulin. Section 4.2 of the SPC was updated accordingly, as well as relevant section of the PL.

### **Reduction of postprandial hyperglycaemia**

The MAH applied for a variation to update section 5.1 of the Summary of Product Characteristics (SPC) regarding data on the reduction of postprandial hyperglycaemia with insulin lispro and lispro Mix25 compared to soluble human insulin and human insulin Mix30/70 respectively. To support its claim the MAH provided data from five published clinical studies comparing postprandial glucose control with Humalog (insulin lispro) and regular human insulin.

The following wording was added to section 5.1 of the SPC for Humalog: “Clinical trials in patients with Type 1 and Type 2 diabetes have demonstrated reduced postprandial hyperglycaemia with insulin lispro compared to soluble human insulin. For fast acting insulins, any patient also on a basal insulin must optimise dosage of both insulins to obtain improved glucose control across the whole day” and the following sentence was added for Humalog Mix25: “Clinical trials in patients with Type 1 and Type 2 diabetes have demonstrated reduced postprandial hyperglycaemia with Humalog Mix25 compared to human insulin mixture 30/70. In one clinical study there was a small (0.38mmol/l) increase in blood glucose levels at night (3.a.m)”.

### **Data on reduction of nocturnal hypoglycaemia**

The MAH requested a variation to include data on reduction of nocturnal hypoglycaemia. To support its claim the MAH provided data from seven clinical studies in patients with Type 1 diabetes, and 2 clinical studies in patients with Type 2 diabetes. On the basis of these studies results, it was concluded that the use of insulin lispro in Type 1 and Type 2 diabetes leads to less nocturnal hypoglycaemia than regular insulin. However, in some studies, reduction of nocturnal hypoglycaemia was associated with increased episodes of daytime hypoglycaemia. This information was included in section 5.1 of the SPC.

### **New data from animal studies**

The MAH applied for a variation to update the SPC regarding data from animal studies on fertility impairment, embryotoxicity or teratogenicity. The MAH provided a review of some studies included in the original dossier aiming to evaluate the overall reproductive performance in animals. The studies showed that insulin lispro did not induced fertility impairment, embryotoxicity or teratogenicity in animals.

### **Use of Humalog in pregnancy**

The MAH applied to amend the SPC regarding clinical experience with insulin lispro in pregnancy. This claim was based on data from three sources (study F3Z-MC-IONS, Pharmacovigilance data and published literature). The statement “data on a large number of exposed pregnancies do not indicate an adverse effect of insulin lispro on pregnancy or on the health of the foetus/newborn”, was included in section 4.6 of the SPC.

### **Update of incompatibilities and instruction for use section of SPC and PL**

The MAH applied for a variation to update sections 6.2 and 6.6 of the SPC and the corresponding sections in the PL to add a warning stating that Humalog should not be mixed with other insulin products.

### **The equipotency of insulin lispro to human insulin**

The MAH applied to include the following sentence in section 5.1 of the SPC:

“Insulin lispro has been shown to be equipotent to human insulin on a molar basis but its effect is more rapid and a shorter duration.”

Previously submitted data from the IMAC study was referred by the MAH to support this claim. Data from IMAC study demonstrated that at different doses, insulin lispro and regular human insulin showed almost identical pharmacokinetics and glucodynamics.

### **Concomitant use of Humalog and monoamine oxidase inhibitors**

The reference that certain antidepressants might reduce insulin requirements was updated with monoamine oxidase inhibitors in section 4.5 of the SPC and PL. Three published papers were cited by the MAH as supporting evidence.