24 July 2014
EMA/CHMP/416253/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humalog

International non-proprietary name: insulin lispro

Procedure No. EMEA/H/C/000088/X/0125

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Humalog
Applicant:	Eli Lilly Nederland B.V. Grootslag 1-5 3991 RA Houten NETHERLANDS
Active substance:	insulin lispro
International Non-proprietary Name/Common Name:	insulin lispro
Pharmaco-therapeutic group (ATC Code):	Insulin lispro (A10AB04)
Therapeutic indication:	For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog is also indicated for the initial stabilisation of diabetes mellitus.
Pharmaceutical forms:	Solution for injection; Suspension for injection
Strength:	100 U/ml and 200 U/ml
Routes of administration:	Intravenous use and Subcutaneous use
Packaging:	cartridge (glass), cartridge (glass) in pre-filled pen and vial (glass)
Package sizes:	1, 2, 5 pre-filled pens of 3 ml and Multipacks containing 10 (2 packs of 5) pre-filled pen of 3 ml

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 3 December 2013 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Humalog 200 U/ml, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 intend c) of the Commission Regulation (EC) No 1234/2008.

Eli Lilly Nederland B.V. is already the Marketing Authorisation Holder for Humalog 100 U/ml.

The applicant applied for an extension of the application for a new strength (200U/ml) for the following indication: the treatment of adults with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog is also indicated for the initial stabilisation of diabetes mellitus.

The legal basis for this application refers to:

The application submitted is composed of administrative information, complete quality data, and a clinical bioequivalent study.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Humalog has been given a Marketing Authorisation in the European Union on 30 April 1996.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 3 December 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2014.
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 June 2014.
- Consultation with Member States, healthcare professionals and patients outcome 03 June 2014.
- During the meeting on 24 July 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Humalog 200 U/ml.

2. Scientific discussion

2.1. Introduction

According to the WHO, the prevalence of obesity in Europe is increasing and contributes towards (up to) 80% of new diagnoses of type 2 diabetes mellitus. There is a correlation between obesity and insulin resistance. Insulin requirements in people with diabetes mellitus and who are obese are higher than the non-obese. Standard insulin injection devices only allow administration of a maximum of 80 units per injection and administration of large volumes (>1 mL) may be associated with pain or discomfort.

One way to manage people with high daily insulin requirements is the development of insulin products with higher strengths than the current 100 U/ml.

Humalog (insulin lispro, rDNA origin) is a human insulin analogue that is a rapid-acting, parenteral blood glucose-lowering agent. Chemically, it is Lys(B28), Pro(B29) human insulin analogue, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Humalog is synthesised in a non-pathogenic laboratory strain of Escherichia coli bacteria that has been genetically altered by the addition of the gene for insulin lispro. The general safety and efficacy of insulin lispro 100 U/mL solution for injection has been established since its first marketing authorisation in the EU on 30 April 1996.

The clinical development program for Humalog 200 U/ml solution for injection was based on the demonstration of bioequivalence to the 100 U/mL formulation.

2.2. Quality aspects

2.2.1. Introduction

This line extension application is for a 200 Units/mL Insulin Lispro, which is double the strength of the currently available Humalog products. The 200 U/ml will be presented only in the form of the prefilled

KwikPen device. The proposed modified KwikPen will contain a total of 600 units of insulin lispro in a prefilled pen injector within a standard 3mL cartridge.

The finished product is a solution, administered as a subcutaneous injection. The formulation differs from the formulation for the 100U strength. It is a solution for injection in a buffer also containing glycerol as a tonicity-modifying agent and metacresol as an anti-microbial preservative.

The KwikPen proposed for the new strength is based on the existing Lilly mechanical, prefilled pen injector device used for the current 100 U/mL Humalog products. The immediate container is a standard 3 ml glass cartridge of identical dimensions and composition as that used for the existing products. To accommodate the 200 U/mL strength with the same cartridge and device dimensions, the pen device mechanism has been modified to allow variable dosing in 0.005 ml/unit increments (compared to 0.010 ml/unit increments in the 100 U/ml KwikPen).

2.2.2. Active Substance

The active substance in Humalog is insulin lispro, a Lys(B28), Pro(B29) human insulin analogue, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Humalog is synthesised in a non-pathogenic laboratory strain of Escherichia coli bacteria that has been genetically altered by the addition of the gene for insulin lispro.

No changes have been introduced to the active substance in this line extension application. Lilly refers to the currently approved Humalog dossier for all quality information related to the active substance, insulin lispro.

It is however noted that procedure EMEA/H/C/000088/WS0353/0113/G with the scope to register a Design Space for the introduction of a post approval change management protocol related to the active substance involving a major change to the manufacturing process for insulin lispro has recently been approved. In the response to the CHMP D120 LOQ Lilly has provided appropriate clarification on how the 200 U/ml strength will be incorporated into the change management protocol in question.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is a 200 U/ml solution for injection and presented as a 3ml cartridge in a sealed single use prefilled pen device which is a modification of the KwikPen currently used for the 100 U/mL range of Lilly insulin and insulin analogue products. It is manufactured and assembled at established insulin analogue manufacturing sites using similar manufacturing methods.

The container closure system is based on that used for the current U-100 product and evaluation of its suitability was carried out and has been found acceptable.

The chosen composition of metacresol as an antimicrobial preservative is the same as that employed for the U-100 Humalog products. The applicant has conducted studies following standard methods to confirm that Insulin with the range of the metacresol content can comply with compendial microbial growth inhibition requirements.

The insulin lispro finished product is contained with a sealed cartridge assembled into a specified pen device. Once assembled, the resulting pen-injector is a sealed unit that cannot be disassembled without physically destroying the pen-injector. Hence it can be assumed that the cartridge may not be readily removed intact limiting the possibility of it being transferred to another device. The design of U-200 product has been found to be an appropriate approach from a safety point of view since the pen injector device is specifically designed only for use with the U-200 product.

Manufacture of the product and process controls

The manufacturing process is based on, and similar to, the one employed for the current U-100 product. Formulation studies were carried out which investigated the robustness of the formulation under processing. Optimisation of the formulation and the manufacturing process was implemented between the clinical and commercial lots. Three lots of final commercial product were then evaluated. The established procedures for preparation of the solution and for sterilisation were found to be suitable for the U-200 product.

Satisfactory details have been provided of the manufacturing process which follows procedures already established for the approved U-100 product. Appropriate validation data has been provided for three commercial scale lots.

The in-process control procedures are considered appropriate for the process and include mixing, dissolution and filling as well as validation of sterile filtration. Aseptic processing and sanitization procedures are satisfactory.

Product specification

The specifications for Insulin lispro 200 U/mL are based on experience with the established Humalog 100 U/mL product including stability testing data.

Satisfactory details of the release testing of the cartridges and the assembled pens have been provided. They are consistent with those applied to the established U-100 strength which is appropriate.

Stability of the product

The submission contains stability data generated from three ~~120L~~ lots of 200 U/mL finished product and packaged in the final commercial immediate container which contains a grey coloured plunger. An ongoing stability study is designed to monitor stability under long term storage conditions for 36 months, under accelerated conditions of 30°C for 3 months and simulated in-use patient conditions.

The stability data provided in the initial submission was insufficient to fully support the requested shelf-life of the product. The Applicant was requested to propose an appropriate shelf life based on real time data. Any bracketing should be adequately justified. This should include, if relevant, data and justification of any extrapolation and commitments to support the stability.

With the responses to the List of questions, Lilly has provided updated real time data in the final container. Additional accelerated data has been provided. Some additional batches have been tested under normal storage conditions up to 36 months. The data provided meets the pre-defined specification and does not indicate any trends which would raise concern. It was concluded that the proposed shelf life of 36 months can be accepted provided that a written commitment regarding ongoing studies is received. The requested commitment has been received.

Adventitious agents

All excipients used comply with the relevant Ph. Eur. requirements. No excipients of animal origin are used.

Conclusions on the chemical, pharmaceutical and biological aspects

The company has provided satisfactory responses to the outstanding quality points and the application is considered approvable. The applicant has submitted a written commitment regarding ongoing stability studies as requested.

2.2.4. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended an additional point for further investigation.

2.3. Clinical aspects

2.3.1. Introduction

The MAH has developed a concentrated version (200 U/ml insulin lispro) of Humalog (currently available as 100 U/ml insulin lispro).

The insulin lispro 200 U/ml clinical trial formulation was based on the commercial Humalog 100 U/ml formulation (insulin lispro 100 U/ml). Changes to the formulation of the established product are:

- increasing the lispro concentration from 100 U/ml to 200 U/ml
- changing the buffering agent from dibasic sodium phosphate to trometamol (hydroxymethyl aminomethane) (TRIS)
- increasing the zinc concentration.

One bioequivalence study (study IOPY) has been submitted in support of the current application. The study was done to establish bioequivalence between two formulations of insulin lispro: insulin lispro phosphate U-100 and insulin lispro TRIS U-200.

The impact of zinc ion concentration changes was previously examined in Study IMAB, submitted as part of the original MAA for Humalog. Study IMAB evaluated the pharmcokinetics and 'glucodynamics' of an insulin lispro formulation with a zinc concentration compared to an insulin lispro formulation without zinc: study IMAB concluded that the impact of zinc was not clinically relevant. The proposed commercial formulation increase in zinc ion concentration in the insulin lispro 200 U/ml formulation is within the range examined in Study IMAB; therefore, it is also not considered clinically relevant.

The company has submitted the following clinical studies in support of this application.

Submission Information	Purpose
Study F3Z-EW-IOPY	Demonstration of the bioequivalence of PK parameters of insulin lispro 200 U/ml (trometamol-buffered) formulation relative to that of insulin lispro 100 U/ml (phosphate-buffered) after subcutaneous administration of 20 units to healthy subjects.
Study F3Z-LC-IMAB	Evaluation of the PK and glucodynamic parameters and the impact of zinc ion concentration.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

2.3.2. Clinical efficacy

2.3.2.1. Main clinical study

One bioequivalence study (study IOPY) has been submitted in support of the current application. The study was done to establish bioequivalence between two formulations of insulin lispro: insulin lispro phosphate U-100 and insulin lispro TRIS U-200.

Title of Study: Evaluation of the Bioequivalence of Two Formulations of Insulin Lispro in Healthy Subjects

Study code: F3Z-EW-IOPY

Study Design: Phase 1, single-centre, open-label, 2-sequence, 4-period, randomised, crossover, 8-hour euglycaemic clamp study.

Methods

- **Study participants**

Eligibility of subjects for study entry was based on the results of a screening medical history, physical examination, clinical laboratory tests and an ECG.

Inclusion criteria

- Healthy subjects, aged 21 – 50yr with a body mass index between 18.5 and 29.9 kg/m^2 inclusive.

Exclusion criteria

- Affiliated to the MAH
- Allergies to insulin or excipients
- 1st degree relative with diabetes mellitus
- a fasting venous blood glucose >6 mmol/L at screening.

- **Treatments**

The study is a phase 1, single-centre, open-label, 2-sequence, 4-period, randomised, crossover, 8-hour euglycemic clamp study to compare the pharmcokinetics and 'glucodynamics' of insulin lispro TRIS U-200 versus insulin lispro phosphate U-100 after s/c administration of 20 U. The treatments were replicated such that each formulation was administered twice on different occasions to healthy subjects over 4 study periods.

Subjects fasted for about 8 hours prior to each dose.

Blood samples were collected over the entire clamp procedure to determine free serum immunoreactive insulin lispro-specific concentrations for PK evaluations.

There was an interval of approximately 4 to 7 days between doses.

- **Objectives**

Primary objective

- To demonstrate the bioequivalence of pharmacokinetic variables ($AUC_{0\text{-tlast}}$ and C_{max}) for the insulin lispro TRIS U-200 formulation relative to that of insulin lispro phosphate U-100 after subcutaneous administration of 20 units to healthy subjects.

Secondary objectives

- To compare other pharmacokinetic variables for insulin lispro TRIS U-200 versus insulin lispro phosphate U-100 after s/c administration.
- To compare the 'glucodynamic' responses for insulin lispro TRIS U-200 versus insulin lispro phosphate U-100 formulation after s/c administration.
- To assess safety and tolerability of insulin lispro TRIS U-200 and insulin lispro phosphate U-100 in healthy subjects.

- **Sample size**

Thirty completers in a replicated treatment design will provide at least 90% power to show the 90% confidence interval of the ratio of means for $AUC_{0\text{-tlast}}$ between the 2 formulations to be within the 0.80 to 1.25 limits.

- **Randomisation**

A randomisation schedule and dosing details for patients was submitted.

- **Blinding (masking)**

The study was open-label. An open-label study design was considered appropriate for a study with pharmacokinetics as the primary endpoint.

- **Statistical methods**

To evaluate bioequivalence between insulin lispro TRIS U-200 relative to insulin lispro phosphate U-100, log-transformed area under concentration parameter estimates (AUC0-$_{tlast}$, AUC_{0-8}) were analysed using a linear mixed-effects model where formulation (TRIS or phosphate), period and sequence were included as fixed factors, and subject as a random factor.

If the 90% CI for treatment ratios (test/reference) for both $AUC_{0-tlast}$ and C_{max} are contained within the range 0.80-1.25, the formulations were considered bioequivalent. A nonparametric approach was taken to evaluate t_{max}, using the Wilcoxon signed-rank test. The difference in median t_{max} between formulations and the 95% CIs for the difference was presented.

To address the secondary objective of comparing glucodynamic variables (G_{tot} and R_{max}) between the U-200 lispro TRIS formulation (test treatment) and the U-100 lispro phosphate formulation (reference treatment), log-transformed G_{tot} and R_{max} estimates were analysed using a linear mixed-effects model where formulation (TRIS or phosphate), period, and sequence were included as fixed factors, and a random effect for subject.

Results

- **Participant flow**

45 healthy men and women were to be enrolled in order that a target of 30 subjects completed the study. Of the 41 subjects who entered the study, 38 were randomly assigned to treatment.

38 healthy subjects, 36 male and 2 female, between the ages of 23 and 45 (with a mean [SD] age of 32.4 [7.1] years) participated in this study and received at least 1 dose of study drug.

36 completed the study and 5 did not complete the study.

4 subjects discontinued due to subject decision: 3 subjects considered the cannulation difficult and / or painful and 1 subject could not commit to the study schedule.

1 subject discontinued due to a protocol violation: the subject's body mass index decreased below the inclusion criteria of 18.5kg/m2 during 2 dosing periods.

- **Recruitment**

Date of first subject entered: 17 May 2010

Date of last subject completed: 23 August 2010

- **Conduct of the study**

There were not any major amendments.

- **Baseline data**

38 healthy subjects, 36 male and 2 female, between the ages of 23 and 45 (with a mean [SD] age of 32.4 [7.1] years) participated in this study. Subject demographics are presented in the following table:

Summary of Demographic and Other Baseline Characteristics for Study F3Z-EW-IOPY

		ABAB	BABA	Overall
Number of subjects studied		20	18	38
Age (years)	Mean	30.4	34.6	32.4
	SD	7.2	6.4	7.1
	Median	28.0	34.5	32.0
	Min	23	23	23
	Max	45	44	45
Sex	Male	20 (100.0%)	16 (88.9%)	36 (94.7%)
	Female	0 (0.0%)	2 (11.1%)	2 (5.3%)
Ethnicity	Hispanic or Latino	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Hispanic or Latino	20 (100.0%)	18 (100.0%)	38 (100.0%)
Race	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	20 (100.0%)	17 (94.4%)	37 (97.4%)
	Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
	White	0 (0.0%)	1 (5.6%)	1 (2.6%)
Weight (kg)	Mean	66.78	66.33	66.57
	SD	6.34	9.42	7.84
	Median	66.55	68.75	67.15
	Min	52.5	45.2	45.2
	Max	78.2	82.3	82.3
Height (cm)	Mean	173.50	169.27	171.49
	SD	5.70	8.36	7.30
	Median	172.75	169.70	172.25
	Min	161.9	154.3	154.3
	Max	184.0	189.0	189.0
Body mass index (kg/m^2)	Mean	22.15	23.04	22.57
	SD	1.31	1.88	1.65
	Median	22.23	23.46	22.59
	Min	19.0	19.0	19.0
	Max	24.2	25.9	25.9

- **Numbers analysed**

41 subjects entered the study, 38 were randomly assigned to treatment, 38 received at least 1 dose of study drug and 36 completed the study.

- **Outcomes and estimation**

Time curves of the arithmetic mean serum concentration of immune-reactive insulin are shown below:

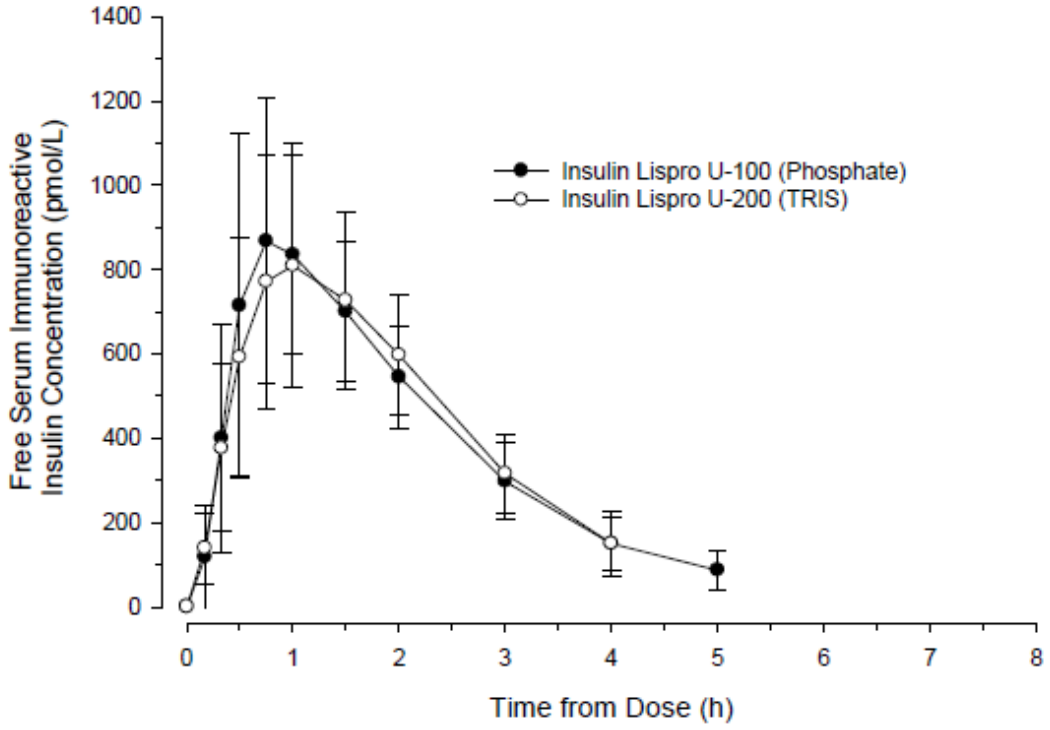

Figure legend: arithmetic mean (± Standard Deviation) serum immunoreactive insulin lispro concentration versus time profiles following the administration of 20 Units of insulin lispro 100 U/ml (U-100 Phosphate) or insulin lispro 200 U/ml (U-200 [TRIS] trometamol).

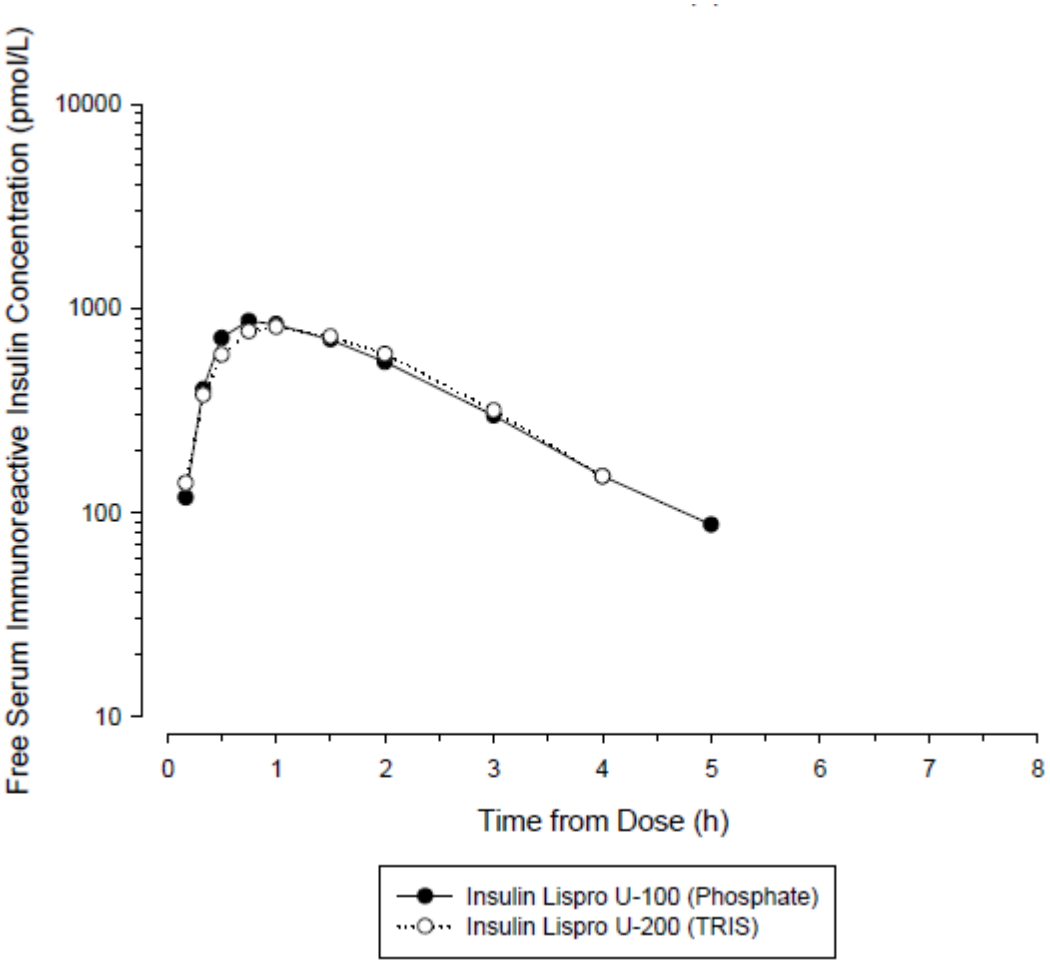

Figure legend: semi-log plot of arithmetic mean serum immunoreactive insulin concentration versus time profiles following the administration of 20 U of Insulin Lispro U-100 (Phosphate) or Insulin Lispro U-200 (TRIS).

Administration of 20 U insulin lispro TRIS U-200 formulation versus insulin lispro phosphate U-100 formulation resulted in similar concentration versus time profiles

The following table summarises the pharmacokinetic variables:

Table IOPY.7.1. Summary of Key Pharmacokinetic Parameters (Geometric Mean [CV%]) of Immunoreactive Insulin Following Administration of 20 U of Insulin Lispro U-100 (Phosphate) or Insulin Lispro U-200 (TRIS)

	Geometric Mean (CV%)	
	Humalog U-100 (Phosphate) (N = 75)	Humalog U-200 (TRIS) (N = 73)
C_{max} (pmol/L)	887 (34)	819 (32)
t_{max} (h)[a]	0.75 (0.50 – 3.00)	1.00 (0.50 – 3.00)
AUC0-t_{last} (pmol•h/L)	1940 (20)	1920 (20)
AUC_{0-8} (pmol•h/L)	2020 (19)	2000 (19)
$AUC_{0-\infty}$ (pmol•h/L)	2030 (19)	2020 (19)
$t_{1/2}$ (h)[b]	0.887 (0.442 – 1.79)	0.794 (0.423 – 2.52)
CL/F (L/h)	58.7 (19)	59.3 (19)
V_Z/F (L)	75.2 (35)	67.9 (39)

[a] Median (Range).
[b] Geometric Mean (Range).

As shown in the following table, the ratio means for AUC(0-8), AUC(0-tlast), AUC(0-∞) and Cmax values were between 0.933 to 0.994. Furthermore, since all of the 90% CIs for the ratios were contained within 0.80-1.25 then the bioequivalence of insulin lispro TRIS U-200 to insulin lispro phosphate U-100 formulation was demonstrated.

Table IOPY.7.2. Statistical Analysis of the Pharmacokinetic Parameters of Serum Free IRI Study F3Z-EW-IOPY

Statistical Analysis of the Pharmacokinetic Parameters of Serum Free IRI for Study F3Z-EW-IOPY

Parameter	Geometric least squares means A	N	n	B	N	n	Ratio of geometric least square means A:B	90% CI for the ratio (Lower, Upper)
AUC (0-8) (pmol*h/L)	2007.738	37	73	2020.292	38	75	0.994	(0.954,1.036)
AUC (0-inf) (obs.) (pmol*h/L)	2020.058	37	73	2034.763	38	75	0.993	(0.952,1.036)
AUC (0-tlast) (pmol*h/L)	1925.269	37	73	1943.936	38	75	0.990	(0.948,1.034)
CMAX (pmol/L)	827.774	37	73	886.906	38	75	0.933	(0.897,0.972)

Model: Log(pk) = sequence + treatment + period + (subject) + (error)
N is the number of subjects
n is the number of observations

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A = Insulin lispro TRIS U-200, 20 U (SC)
B = Insulin lispro phosphate U-100, 20 U (SC)

The CHMP acknowledged that the 90% confidence intervals for Cmax and AUC are within the 80 – 125 limits and so are consistent with bioequivalence between the two formulations.

Estimates of between- and within-subject variability by formulation are presented in the following table:

Table IOPY.7.4. Variability Estimates of the Pharmacokinetic Parameters for Serum Free IRI Study F3Z-EW-IOPY

PRODUCTION DATA - PRODUCTION MODE
Table IOPY.x Variability Estimates of the Pharmacokinetic Parameters for Serum Free IRI for Study F3Z-EW-IOPY

		CV% (90% CI)	
Parameter	Treatment	Within-Subject	Between-Subject
CMAX (pmol/L)	A	14.5 (12.1,18.1)	29.6 (24.1,38.7)
	B	17.5 (14.6,21.8)	29.5 (23.9,39.1)
AUC (0-tlast) (pmol*h/L)	A	13.9 (11.5,17.6)	15.0 (11.6,22.0)
	B	12.2 (10.2,15.3)	15.4 (12.3,21.1)
AUC (0-inf) (obs.) (pmol*h/L)	A	12.6 (10.4,15.9)	14.4 (11.2,20.7)
	B	11.5 (9.6,14.5)	14.4 (11.4,19.7)
AUC (0-8) (pmol*h/L)	A	12.6 (10.4,15.9)	14.7 (11.5,21.0)
	B	11.4 (9.5,14.3)	14.6 (11.6,19.9)

Model: Log(PK) = sequence + treatment + period + (subject) + (error)
A = Insulin lispro TRIS U-200, 20 U (SC)
B = Insulin lispro phosphate U-100, 20 U (SC)

Additional analyses were done which excluded a subject who had a low body mass index according to the study entry criteria and the conclusions did not change.

- **Ancillary analyses**

Administration of 20 U insulin lispro TRIS U-200 formulation versus insulin lispro phosphate U-100 formulation resulted in comparable glucose infusion rate versus time profiles, as shown in the following figure:

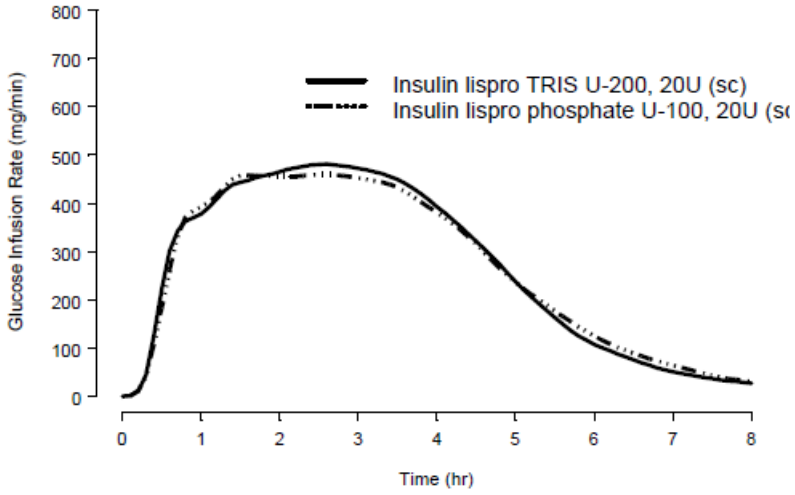

Figure IOPY.7.2. Arithmetic mean glucose infusion rate versus time profiles following the administration of 20 U of Insulin Lispro U-100 (Phosphate) or Insulin Lispro U-200 (TRIS)

Pharmacodynamic variables also showed similar results, as shown in the following table:

Table IOPY.7.5. **Summary of Key Glucodynamic Parameters (Geometric Mean [CV%]) Following Administration of 20 U of Insulin Lispro U-100 (Phosphate) or Insulin Lispro U-200 (TRIS)**

	Geometric Mean (CV%)	
	Humalog U-100 (Phosphate) (N = 75)	Humalog U-200 (TRIS) (N = 73)
R_{max} (mg/min)	539 (27)	544 (23)
tR_{max} (h)	2.00 (56)	2.11 (49)
Early tR_{max50} (h)	0.595 (29)	0.568 (31)
Late tR_{max50} (h)	4.34 (42)	4.39 (37)
tR_{onset} (h)	0.350 (43)	0.337 (34)
tR_{last} (h)	7.12 (15)	7.04 (14)
G_{tot} (g)	123 (30)	125 (25)

Gtot, total glucose infused throughout the clamp

Rmax, maximum glucose infusion rate

tRmax, time of maximum glucose infusion rate

Estimates of between- and within-subject variability by formulation are presented in the following table:

Table IOPY.7.8. **Variability Estimates of the Glucodynamic Parameters Study F3Z-EW-IOPY**

PRODUCTION DATA - PRODUCTION MODE

Table IOPY.x Variability Estimates of the Glucodynamic Parameters for Study F3Z-EW-IOPY

		CV% (90% CI)	
Parameter	Treatment	Within-Subject	Between-Subject
GTOT (g)	A	10.5 (8.8,13.0)	22.7 (18.6,29.4)
	B	13.9 (11.7,17.3)	26.3 (21.5,34.4)
RMAX (mg/min)	A	17.2 (14.4,21.5)	16.2 (12.2,24.5)
	B	12.9 (10.8,16.1)	23.3 (19.0,30.5)

Model: Log(GD) = sequence + treatment + period + (subject) + (error)
A = Insulin lispro TRIS U-200, 20 U (SC)
B = Insulin lispro phosphate U-100, 20 U (SC)

- **Summary of main results**

Table: Pharmacokinetic parameters for insulin lispro (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	geometric mean	CV%	geometric mean	CV%
$AUC_{(0\text{-}tlast)}$ $AUC_{(0\text{-}8h)}$	1920 pmol.h/L 2000 pmol.h/L	20 19	1940 pmol.h/L 2020 pmol.h/L	20 19
$AUC_{(0\text{-}\infty)}$	2020 pmol.h/L	19	2030 pmol.h/L	19
C_{max}	819 pmol/L	32	887 pmol/L	34
T_{max}*	1.0hr (median)	0.5-3.0 (range)	0.75hr	0.5 – 3.0
$AUC_{0\text{-}tlast}$ area under the plasma concentration-time curve from time zero to tlast $AUC_{0\text{-}8h}$ area under the plasma concentration-time curve from time zero to 8 hours> $AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max} time for maximum concentration (* median, range)				

Table: Statistical analysis for insulin lispro (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals
$AUC_{(0\text{-}8)}$	0.994	0.954, 1.036
$AUC_{(0\text{-}tlast)}$	0.993	0.952, 1.036
$AUC_{(0\text{-}\infty)}$	0.990	0.948, 1.034
C_{max}	0.933	0.897, 0.972

2.3.2.2. Supportive studies

The company referred in this application to study IMAB, submitted as part of the original MAA for Humalog. Study IMAB evaluated the pharmacokinetics and glucodynamics of an insulin lispro formulation with zinc compared to an insulin lispro formulation without zinc. The company has concluded that zinc content, as described in IMAB, did not affect the release kinetics of insulin lispro into the general circulation.

In addition, a validation study of a method for the determination of free Lispro Insulin in human serum by radio-immunoassay was submitted by the MAH.

2.3.3. Conclusions on clinical efficacy

Study IOPY was a phase 1, single-centre, open-label, 2-sequence, 4-period, randomised, crossover, 8-hour euglycemic clamp study carried out to establish bioequivalence between insulin lispro TRIS U-200 and insulin lispro phosphate U-100. 38 subjects received one or more doses of study drug and 36 subjects completed the study.

The CHMP was of the view that the design and conduct of study IOPY are acceptable.

Statistical analysis of Cmax and AUC for insulin lispro TRIS U-200 and insulin lispro phosphate U-100 returned results within the 80 – 125 confidence interval limits.

Based on the presented bioequivalence study IOPY, insulin lispro TRIS U-200 may be considered bioequivalent with insulin lispro phosphate U-100.

2.4. Clinical safety

Patient exposure

38 subjects received one or more doses of study drug in the submitted clinical trials.

Adverse events

None of the 38 subjects who received one or more doses of study drug reported adverse events that were related to study drug as judged by the investigator. The most common adverse events were catheter site haematoma (11 subjects) and procedural-site reaction (5 subjects). Most adverse events were of mild severity, 2 events were considered moderate (1 catheter site haematoma in each treatment group) and none was considered severe. Records of fluctuations in vital signs were not considered to be clinically significant.

Serious adverse event/deaths/other significant events

Deaths and serious adverse events did not occur.

Laboratory findings

There were not any clinically-significant alterations in laboratory or urinalysis results.

Discontinuation due to adverse events

Discontinuation because of an adverse event did not occur.

2.4.1. Discussion on clinical safety

The MAH recognised that medication errors (between both doses) are the main potential risk. However, the MAH considered that these errors are limited to a misuse of the product. The MAH identified two possible scenarios that could lead to medication errors: (i) extraction of the 200 U/mL solution from a dedicated pen and administration by a different delivery system and (ii) carrying out an unnecessary dose conversion when changing from 100 U/mL to 200 U/mL or vice versa. These have been adequately addressed by labelling of the new strength and a communication plan (Dear Healthcare Professional Communication and Patient Communication) has been developed as described in the Risk Management Plan.

2.4.2. Conclusions on the clinical safety

During the course of the study, there were not any adverse events that were considered to be related to study drug and there were not any clinically-significant alterations in vital signs or laboratory results. Within the study, both formulations of insulin lispro appeared to be well-tolerated and safe.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.6. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5 is acceptable. The PRAC advice is attached.

The CHMP endorsed the Risk Management Plan version 5 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	• Hypoglycaemia • Hypersensitivity • Oedema leading to congestive heart failure when insulin lispro is used concomitantly with thiazolidinediones
Important Potential Risks	• Medication errors, including those associated with the potential misuse of the proposed Humalog 200 U/ml KwikPen. • Antigenicity • Neoplasms
Missing Information	• Change in the incidence of hypersensitivity, immunogenicity or Lack of Drug Effect (LODE) with the proposed new manufacturing process (sKPB) • Change in the incidence of hypersensitivity adverse reactions, Immunogenicity, local, injection-site adverse reactions, Reduced efficacy/ inadequate response to therapy (LODE) or Hypoglycemia with the protamine sourced from a different location (Hokkaido)

The PRAC agreed on the safety concerns as proposed in this version of the RMP.

Pharmacovigilance plan

Table 2.2: Ongoing and planned studies in the PhV development plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Post approval Safety Surveillance (sKPB) A post-approval safety surveillance program for monthly Lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity and immunogenicity events (surveillance, Category 3)	To evaluate any potential change in the frequency of hypersensitivity, immunogenicity or lack of drug effect (LoDE) events	Changes in the frequency of hypersensitivity and immunogenicity events with the altered manufacturing process	Planned after the changes in manufacturing have been approved and insulin lispro produced according to the new process becomes available	A 6-monthly cumulative analysis or any monthly assessment that identifies a possible drug event combination (DEC) that might indicate a manufacturing-related event after appropriate signal analysis and clarification shall be forwarded to the relevant authority agency within 15 days of completion, or as otherwise requested. The evaluation shall be executed as described for a period not-less-than 3 years following the expiry of the first released finished batch incorporating insulin lispro manufactured using the proposed process.
<u>US Only:</u> **Protamine Source** Post-approval safety surveillance program for Lot-specific adverse event review and analysis (surveillance, category 3)	To determine any increase in the frequency of specific adverse events reported in patients receiving insulin lispro containing Hokkaido-sourced protamine when compared to the frequency previously observed Honshu-sourced protamine.	Changes in the incidence of hypersensitivity adverse reactions, immunogenicity or local, injection-site adverse reactions. Changes in the incidence of reports of reduced efficacy or inadequate response to therapy (LoDE). Changes in the incidence of hypoglycemia.	Started[1]	Quarterly and annual cumulative reports will be forwarded to the FDA within 30 days of completion. The first report was submitted by 15 August 2013

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

In addition to the studies listed in this Pharmacovigilance plan, the Applicant has committed to submitting a protocol synopsis within one month after Commission Decision of the U200 strength, and to submit a full protocol within 6 months after Commission Decision, for a study examining the effectiveness of risk minimization. The study objectives are to assess the receipt, perception and comprehension of key messages relating to all potential medication errors, as well as impact on behaviour.

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan, together with the study the Applicant has committed to regarding measuring the effectiveness of risk minimisation measures, are sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Table V.2. **Summary of Risk Minimisation Measures**

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Hypoglycaemia	**SPC 4.3: Contraindications** Hypoglycaemia is listed as a contraindication. **SPC 4.4: Special Warnings and Precautions for Use** Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include: long duration of diabetes;	None.

	intensified insulin therapy; diabetic nerve disease; or medications such as beta-blockers. A few patients who have experienced hypoglycaemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin. Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death. Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia. A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin. **SPC 4.7 Effects on Ability to Drive and Use Machines** The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving; this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia, or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances. **SPC 4.8 Undesirable Effects** Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia is a result of both the insulin dose and other factors, e.g., a patient's level of diet and exercise.	

	SPC 4.9 Overdose Insulins have no specific overdose definitions because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability, and other metabolic processes. Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure. Hypoglycaemia may be associated with listlessness, confusion, palpitations, headache, sweating, and vomiting. Mild hypoglycaemic episodes will respond to oral administration of glucose or other sugar or saccharated products. Correction of moderately severe hypoglycaemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously. If the patient is comatose, glucagon should be administered intramuscularly or subcutaneously. However, glucose solution must be given intravenously if glucagon is not available or if the patient fails to respond to glucagon. The patient should be given a meal as soon as consciousness is recovered. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.	
Hypersensitivity	**SPC 4.3 Contraindications** Hypersensitivity to insulin lispro or to any of the excipients. **SPC 4.8 Undesirable Effects** Local allergy in patients is common (1/100 to <1/10). Redness, swelling, and itching can occur at the site of insulin injection. This condition usually resolves in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. Systemic allergy, which is	None

	rare (1/10,000 to <1/1,000) but potentially more serious, is a generalised allergy to insulin. It may cause a rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalised allergy may be life-threatening.	
Oedema leading to CHF (with TZD)	**SPC 4.4 Special Warnings and Precautions for Use** Combination of Humalog with pioglitazone: Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Humalog is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. **SPC 4.8 Undesirable Effects** Cases of oedema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy.	None
Medication Errors	Comprehensive instructions for use, unambiguous packaging, and user training are fundamental activities, intended to reduce the risk of medication errors to the lowest possible level.	**In general**: None Specific for Humalog 200 U/ml KwikPen: A Direct Healthcare Professional Communication (DHPC) will be distributed to those HCPs most likely to prescribe insulin as applicable for each country and as agreed with the National Competent Authorities; for example endocrinologists, diabetologists, general practitioners, and diabetes nurses. A communication to patients via their prescribing HCP at the time of their first prescription. An affixed warning message stating "Use only in this pen or

		serious overdose can result" is included on packaging and included information.
Antigenicity	None	None
Neoplasms	None	None

Abbreviations: CHF = congestive heart failure; SPC = Summary of Product Characteristics; TZD = thiazolidinediones.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.7.2. Additional expert consultation

During the evaluation procedure for Humalog 200 U/ml concerns were raised with regards to the introduction of the new strength, and whether sufficient measures had been put in place to ensure the safe and correct use of the new high strength concentration. As such a Healthcare Professional and Patient Organisation consultation was launched to request feedback on how to minimise the risk of medication errors with this new strength for Humalog. The comments received in this consultation prompted the PRAC and CHMP to request further changes to the labelling (mainly to clearly differentiate both strengths). The MAH adequately addressed these concerns by amending the labelling and by other measurements described in the risk minimisation plan.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Insulin lispro 100 U/mL is a well-understood, extensively-studied product with an established positive benefit-risk ratio that has been marketed in the EU since 1996. The company has developed a 200 U/mL formulation. The company intends the current product to be used by those people with diabetes mellitus who need >20U insulin at mealtime.

The MAH has submitted study IOPY to claim bioequivalence between the 100 U/mL formulation of insulin lispro and the new 200 U/mL formulation. The company anticipates that because the insulin lispro 200 U/ml formulation is bioequivalent to the currently marketed insulin lispro 100 U/ml formulation then the therapeutic benefit-risk ratio (incorporating the known beneficial effects) of the insulin lispro 100 U/ml formulation may also be claimed for the 200 U/mL product.

A dedicated device has been developed to administer the new formulation. The company has carried out human factors engineering and usability testing on the 200 U/mL KwikPen device following scientific advice from the FDA and by following published guidance from the FDA.

Testing was carried out on subjects with diabetes mellitus, physicians and nurses (each group given its own set of scenarios).

Uncertainty in the knowledge about the beneficial effects

Study IOPY was a study of bioequivalence carried out on healthy volunteers, none of whom was clinically obese. Insulin lispro 200 U/mL has not (apparently) been studied in people with diabetes mellitus, obese or not. The human factors engineering and usability testing on the 200 U/mL KwikPen device was carried out in an office environment and involved simulation of injections. There is not, at present, any clinical knowledge of beneficial effects in the population of people with diabetes mellitus either arising from exposure to insulin lispro 200 U/mL or from using the newly developed administration device.

The company claims of potential benefit are based on the company's own expertise, consultations with advisory boards, market research and published literature.

Risks

Unfavourable effects

The company anticipates that because the insulin lispro 200 U/ml formulation is bioequivalent to the currently marketed insulin lispro 100 U/ml formulation then the therapeutic benefit-risk ratio (incorporating the known unfavourable effects) of the insulin lispro 100 U/ml formulation may also be claimed for the 200 U/mL product.

The company recognises that medication errors are the main potential risk and considers that these are limited to a misuse of the product. The company has identified two possible scenarios: (i) extraction of the 200 U/mL solution from a dedicated pen and administration by a different delivery system and (ii) carrying out an unnecessary dose conversion when changing from 100 U/mL to 200 U/mL or vice versa. These have been addressed by labelling and other measurements described in the risk minimisation plan.

Uncertainty in the knowledge about the unfavourable effects

Study IOPY was a study of bioequivalence carried out on healthy volunteers, none of whom was clinically obese. Insulin lispro 200 U/mL has not (apparently) been studied in people with diabetes mellitus, obese or not. There is not, at present, any clinical knowledge of unfavourable effects in the population of people with diabetes mellitus either arising from exposure to insulin lispro 200 U/mL or from using the newly developed administration device.

Benefit-risk balance

Importance of favourable and unfavourable effects

On the basis of bioequivalence between insulin lispro 100 U/mL and insulin lispro 200 U/mL, it is acknowledged that it is reasonable to assume that the importance of the favourable and unfavourable effects of exposure to the 200 U/mL formulation of insulin lispro will reflect those already established for the 100 U/mL formulation.

The dedicated 200 U/mL KwikPen device has been developed from the 100 U/mL KwikPen device (in clinical use for many years).

Although the human factors engineering and usability testing on the 200 U/mL KwikPen device was carried out in an office environment (and not in situations reflecting real life), this may be accepted because of knowledge of experience of the 100 U/mL KwikPen device used with insulin lispro 100 U/mL.

The goal of human factors engineering in medical device design development is to ensure that the device will be safe and effective to use. The company identified the intended users of the 200 U/mL KwikPen device and the tasks they had to perform to use the device effectively. Hazards were identified and eliminated or controlled and informed the proposed risk management plan. As a consequence, a formal clinical study of use has not been submitted.

Benefit-risk balance

On the basis of bioequivalence between the insulin lispro 100 U/ml formulation and the insulin lispro 200 U/ml formulation, the positive benefit-risk balance of the insulin lispro 100 U/ml formulation may also be claimed for the insulin lispro 200 U/ml formulation. Risks associated with the new formulation and KwikPen device have been identified and addressed by the human factor engineering study. The benefit risk balance of Humalog 200 U/ml is therefore considered to be positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Humalog 200 U/ml in the "treatment of adults with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog 200 units/ml KwikPen is also indicated for the initial stabilisation of diabetes mellitus" is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent

updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide a Dear Healthcare Professional Letter (DHPC) and patient communication prior to launch targeting all physicians and nurses who are expected to be involved in the treatment and management of diabetic patients and, where required, all pharmacists who are expected to dispense Humalog.

The target audience and the modalities for distribution all of these materials are to be agreed at Member State level. The MAH shall agree the final text of the Dear Healthcare Professional Communication letter and the content of the patient communication together with a communication plan, with the National Competent Authority in each Member State prior to launch of the product.

The DHPC and patient communication are aimed at increasing awareness about the fact that Humalog is now available in two strengths and describing key differences in the design of the packages and the prefilled pen devices to minimise the risk of medication errors and mix up between the two different strengths of Humalog.

The MAH shall ensure that healthcare professionals are informed that all patients who have been prescribed Humalog should be trained on the correct use of the prefilled pen before prescribing or dispensing Humalog.

The DHPC should address the following key elements:

- Humalog is now available in 2 strengths
- Key features of the design of the package and prefilled pen device
- When prescribing, to ensure that the correct strength is mentioned on the prescription
- Humalog should not be used outside of the prefilled pen device
- Dose conversion on switching from Humalog U-100 to U-200 should not be performed
- Medication errors or any side effects should be reported

The patient communication should address the following key elements:

- Humalog is now available in 2 strengths
- Key features of the design of the package and prefilled pen device

- Humalog should not be used outside of the prefilled pen device
- Dose conversion on switching from Humalog U-100 to U-200 should not be performed
- Check the number of units dialled before injecting
- Check the name, type and strength of insulin dispensed
- Reporting of medication errors or any side effects