

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-017
21-018

PHARMACOLOGY REVIEW(S)

/S/

FEB 22 1999

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Insulin analog, Acute toxicology,

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Pharmacology Team Leader
Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP).
HFD#510
Review Completion Date: February 22, 1999.
Review number: 1

IND/NDA NUMBER: 21-017

Serial number/date/type of submission: New NDA December 22, 1998

Information to sponsor: Yes () No (X)

Sponsor (or agent): Eli Lilly and Co.; Lilly Corporate Center; Indianapolis, IN 46285

DRUG

Code Name: LY275585[P]

Generic Name: Insulin lispro protamine suspension

Trade Name: Humalog® Mix 25™ [Insulin lispro 25% and 75% insulin lispro protamine suspension (rDNA origin)]

Chemical Name: Insulin lispro 25% and 75% insulin lispro protamine suspension (rDNA origin)

Molecular Formula/-Molecular Weight: Humalog® has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

Structure: Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed.

Relevant INDs/NDAs/DMFs: NDA 20-563, Humalog®. Approved June 14, 1996; IND [redacted]
Pending NDA 21-018 for a Humalog® 50% mix similar to this application.

Drug Class: Insulin analog, recombinant human protein.

Indication: Treatment of hyperglycemia.

Clinical formulation:

Insulin Lispro Low and Mid Mixtures, 100 U/mL, 10 mL Vials and 3.0 mL Cartridges

	QUANTITY/mL LOW MIXTURE	QUANTITY/mL MID MIXTURE
<u>Active ingredient:</u>		
Lys-Pro Insulin (Insulin Lispro)	100 U	100 U
<u>Other Ingredients:</u>		
Dibasic Sodium Phosphate, USP	3.78 mg	3.78 mg
Glycerin, USP	16.00 mg	16.00 mg
l-Phenol, USP		
Metacresol, USP		
Protamine Sulfate, USP	0.28 mg	0.19 mg
Zinc Oxide, USP	q.s. for content of 0.025 mg Zn ⁺⁺ content	q.s. for content of 0.0305 mg Zn ⁺⁺ content
Hydrochloric Acid Solution 10%	qs	qs
Sodium Hydroxide Solution 10%	qs	qs
Water for Injection, USP		
[redacted]		

Route of administration: Injectable, SC

Proposed clinical protocol or Use: As a rapid acting insulin analog for administration 15 minutes prior to a meal. This is described as a Lispro low mixture and Lispro mid mixture which vary slightly in contents of protamine sulfate, metacresol, phenol and zinc oxide.

Disclaimer – use of sponsor's material: Sponsor data tables are reproduced in this report.

INTRODUCTION AND DRUG HISTORY: The active ingredient of Humalog® was approved June 14, 1996. This is an analog of human insulin in which the natural sequence of proline and lysine in positions B28 and B29 have been reversed. Upon injection, the [redacted] of insulin lispro dissociates into monomer form more rapidly than human insulin. Thus, lispro insulin is marketed as a rapid-acting insulin. The present submission provides for new formulations of this product to provide a sustained release preparation, which is analogous to human insulin NPH and provides a longer action profile. Three formulations have been studied clinically referred to as Insulin Lispro Low, Mid and [redacted] mixtures which have the ratios of insulin lispro: NPL of 1:3, 1:1 and [redacted] respectively. It is expected that the Low and Mid mixtures would provide an intermediate-acting plasma insulin profile similar to those provided by human regular/NPH mixtures. In addition, a better postprandial glucose control is expected as a result of the rapid action of the lispro component. Investigational formulations differed slightly from the commercial formulations in quantities of protamine sulfate, metacresol and [redacted] phenol, each of which are slightly increased in the Commercial formulation, but within safe limits for the use of these inactive ingredients. The primary difference of this product compared to the approved Lispro product is that of the time-action profile. Given the extensive preclinical work done for the original NDA 20-563, limited preclinical studies have been provided in this NDA. The primary concerns with this product are the timing and effectiveness in the clinical population as well as the potential for antigenicity. Pivotal studies to determine the activity profile have been done in humans. The toxicity profile of most insulin products relates to the limitations of dosing due to severe hypoglycemia. Therefore, extensive preclinical studies of this product were not necessary.

Studies reviewed within this submission:

		Page #
I.	Nonclinical Pharmacology Report 1: Comparison of Insulin Lispro Protamine in Suspension (NPL) with NPH Human insulin in Rabbit Blood Glucose-Lowering Tests	3
II.	Nonclinical Pharmacology Report 2: Comparative Dynamics of Neutral Protamine Lispro (NPL) and NPH Human Insulin in Dogs	4
III.	Toxicology Report 29: The Acute Toxicity of LY275585 Administered Subcutaneously to Fischer 344 Rats	5

Studies not reviewed within this submission: None.

APPEARS THIS WAY
ON ORIGINAL

PHARMACOLOGY:

General Comments: The purpose of the following studies was to compare the new Lispro Insulin formulations to approved similar insulin products of NPH Human Insulin. These studies were intended to determine whether the properties of insulin lispro are altered by the co-crystallization with protamine.

Study Title: Comparison of Insulin Lispro Protamine in Suspension (NPL) with NPH Human Insulin in Rabbit Blood Glucose-Lowering Tests

Study No: Nonclinical Study Report 1

Amendment #, Vol. #, and page #: Original NDA vol. 30 Page 15.

Conducting laboratory and location: Lilly Research Laboratories; Indianapolis, IN 46285

Date of study initiation: Studies listed as performed on September 22 and 23, 1993.

GLP compliance: Not stated.

QA- Report Yes () No (X)

METHODS:

Dosing: Subcutaneous dosing

species/strain: Rabbit

#/sex/group or time point: 20 or 8 (two experiments). Sex not specified.

age: not provided

weight: not provided

dosage groups in administered units: NPH and NPL insulin suspensions were tested in two separate experiments on consecutive days.

route, form, volume, and infusion rate: SC injections of 0.2 U/kg of Humulin N and two different NPL preparations of 0.2 U/kg.

Drug, lot#, radiolabel, and % purity: NPH lot 6NM76A; NPL lots 9-14-1 and 9-14-2.

Formulation/vehicle: Not specified. Probably similar to clinical preparations.

OBSERVATIONS AND TIMES: Blood glucose levels were taken on samples taken at time 0, 0.5, 1.0, 2.0, 4.0 and 6 h after injection.

RESULTS:

Table 1: Blood glucose levels (mg/mL) in rabbits following SC injection (0.2 U/kg) of Humulin N and two different NPL preparations (n=20)

TIME (h)	9/22/93 experiment (n=20)		9/23/93 experiment (n=8)	
	NPH	NPL	NPH	NPL
0	82.9	86.2	84.4	85.4
0.5	47.2	48.6	55.2	56.3
1	45.8	49.6	63.0	63.4
2	54.0	66.1	76.5	76.9
4	75.7	82.0	84.1	82.4
6	78.7	81.3	nd	nd

KEY STUDY FINDINGS:

The time-action profiles for lowering of blood glucose for NPH and NPL were similar.

Study Title: Comparative Dynamics of Neutral Protamine Lispro (NPL) and NPH Human Insulin in Dogs

Study No: Nonclinical Study Report 2

Amendment #, Vol. #, and page #: Original NDA vol. 30 Page 40.

Conducting laboratory and location: Lilly Research Laboratories; Indianapolis, IN 46285

Date of study initiation: Series of experiments conducted between December 3, 1993-April 8, 1994.

GLP compliance: Not stated.

QA- Report Yes () No (X)

METHODS:

Dosing: Subcutaneous dosing 0.5 U/kg

species/strain: Dog (conscious, fasted 18 h)

#/sex/group or time point: 6 mongrel dogs were used in these studies. Each received NPL and NPH on different occasions.

age: not provided

weight: 15-25 kg

dosage groups in administered units: NPH and NPL insulin suspensions were tested in several experiments at 0.5 U/kg. See tables for groups. There was a concurrent infusion of 20% glucose to maintain a basal fasting glucose rate (glucose clamp).

route, form, volume, and infusion rate: SC injections of 0.5 U/kg of Humulin N and NPL.

Drug, lot#, radiolabel, and % purity: NPH lot N1A52D; NPL lot 2NZ160LPP152.

Formulation/vehicle: Not specified. Probably similar to clinical preparations.

OBSERVATIONS AND TIMES: Blood samples were taken at various time points as follows:

5 minute intervals for 45 minutes (45 min)

every 10 minutes for 40 minutes (85 min)

every 15 minutes for 30 minutes (115 min)

every 20 minutes for 40 minutes (155 min)

every 25 minutes for 150 minutes (305 min)

every 30 minutes until the end of the study (at least 8 h).

Immunoreactive insulin (IRI) levels were determined using [redacted] which detect both human insulin and lispro.

RESULTS:

Kinetic parameters for NPL and NPH

Parameter	NPL	NPH
C_{max} (ng/mL)	2.61 ± 0.22	2.58 ± 0.36
T_{max} (min)	93 ± 22	145 ± 33
Insulin area (ng•min/mL)	810 ± 71	680 ± 77

Pharmacodynamic parameters for NPL and NPH

Parameter	NPL	NPH
R_{max} (mg/kg-min)	10.8 ± 1.2	13.2 ± 1.9
T_{Rmax} (min)	277 ± 58	265 ± 38
Total glucose infused (g/kg)	3.35 ± 0.41	3.8 ± 0.65

KEY STUDY FINDINGS:

1. Insulin lispro protamine suspension had a similar kinetic and dynamic responses to those of NPH.
2. There were no statistically significant differences between the glucose response curves for the two products.
3. The time at which maximum insulin/insulin lispro concentration was reached was slightly different in the two preparations. This did not lead to any significant alteration in the response of glucose requirements between the two products.
4. The glucose requirements for NPL appeared to plateau for ~ 4.5 h.

TOXICOLOGY:

Study Title: The Acute Toxicity of LY275585 Administered Subcutaneously to Fischer 344 Rats

Study No: Toxicology Report 29, Study R17194

Amendment #, Vol. #, and page #: Initial NDA vol. 30 Page 77.

Conducting laboratory and location: Lilly Research Laboratories; Indianapolis, IN 46285

Date of study initiation: May 19, 1994.

GLP compliance: Yes

QA- Report Yes () No (X)

METHODS:

Dosing: SC

species/strain: Fischer 344 rats (non-fasted).

#/sex/group or time point: 5/sex/group.

age: ~ 8-9 weeks.

weight: males: 190.5 ± 5.6 g, females: 139.8 ± 4.0 g

dosage groups in administered units: control and 10 U/kg groups; 1 ml/kg.

route, form, volume, and infusion rate: SC

Drug, lot#, radiolabel, and % purity: CT03280, 100 U/ml. Bulk lot 382EM3

Formulation/vehicle: formulation in Humulin® BR Diluent pH 7.3

OBSERVATIONS AND TIMES:

Clinical signs: 1 h intervals for the first 6 hours post dosing, then daily up to 2 weeks.

Body weights: weekly.

Gross pathology: Examination of all external body surfaced and orifices, and the thoracic and abdominal cavities and their viscera.

RESULTS:

Clinical signs: No treatment related signs.

Body weights: No treatment-related effects.

Gross pathology: No treatment-related effects.

KEY STUDY FINDINGS:

1. Animals were apparently not dosed to the limits to demonstrate hypoglycemia in clinical signs. No toxicological effects were noted in the parameters observed.

OVERALL SUMMARY AND EVALUATION:

Introduction: The active ingredient of Humalog® was approved June 14, 1996. This is an analog of human insulin in which the natural sequence of proline and lysine in positions B28 and B29 have been reversed. Upon injection, the [redacted] of insulin lispro dissociates into monomer form much more rapidly than human insulin. Thus, lispro insulin is marketed as a rapid-acting insulin. The present submission provides for new formulations of this product to provide a sustained release preparation, which is analogous to human insulin NPH and provides a longer action profile than the currently approved formulation. Three formulations have been studied clinically referred to as Insulin Lispro Low, Mid and [redacted] mixtures which have the ratios of insulin lispro: NPL of 1:3, 1:1 and [redacted] respectively. It is expected that the Low and Mid mixtures would provide an intermediate-acting plasma insulin profile similar to those provided by human regular/NPH mixtures. In addition, a better postprandial glucose control is expected as a result of the rapid action of the lispro component. Investigational formulations differed slightly from the commercial formulations in quantities of protamine sulfate, metacresol and [redacted] phenol, each of which are slightly increased in the Commercial formulation, but within safe limits for the use of these inactive ingredients. The primary difference of this product compared to the approved Lispro product is that of the time-action profile. Given the extensive preclinical work done for the original NDA 20-563, limited preclinical studies have been provided in this NDA. The primary concerns with this product is the timing and effectiveness in the clinical population and the potential for antigenicity. Pivotal studies to determine the activity profile have been done in humans. The toxicity profile of most insulin products relates to the limitations of dosing due to severe hypoglycemia. Therefore, extensive preclinical studies of this product were not necessary.

Safety Evaluation: The primary preclinical issue for this product is the time-action profile of activity. The systemic toxicity of lispro insulin has been well characterized and is, in general similar to native insulin. Assuming that the new mix is stable in a patient setting, there should be no unexpected toxicity with the proposed mixtures.

Conclusions: The preclinical studies provided by the sponsor indicate that the proposed mixtures appear to have the predicted prolonged activity. There should be no unexpected toxicity with these mixtures. The key data for determining approvability will come from the pivotal human trials to determine action profile and antigenicity in humans. From a pharmacology standpoint, this NDA supplement is APPROVED.

COMMUNICATION REVIEW:

Labeling Review (NDA): Preclinical sections of the label are identical to current labeling for Humalog®. Labeling is acceptable. No changes are required for the preclinical sections of the label.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATIONS:

Internal comments: AP

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

[Redacted Signature] /S/ 2/22/9

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: IND
HFD510
HFD510/Steigerwalt/JRhee
Review Code: AP

**APPEARS THIS WAY
ON ORIGINAL**

FEB 22 1999

TS/

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Insulin analog, Acute toxicology,

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Pharmacology Team Leader
Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)
HFD#510
Review Completion Date: February 22, 1999.
Review number: 1

IND/NDA NUMBER: 21-018

Serial number/date/type of submission: New NDA December 22, 1998

Information to sponsor: Yes () No (X)

Sponsor (or agent): Eli Lilly and Co.; Lilly Corporate Center; Indianapolis, IN 46285

DRUG

Code Name: LY275585[P]

Generic Name: Insulin lispro protamine suspension

Trade Name: Humalog® Mix 50™ [Insulin lispro 50% and 50% insulin lispro protamine suspension (rDNA origin)]

Chemical Name: Insulin lispro 50% and 50% insulin lispro protamine suspension (rDNA origin)

Molecular Formula/ Molecular Weight: Humalog® has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

Structure: Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed.

Relevant INDs/NDAs/DMFs: NDA 20-563, Humalog®. Approved June 14, 1996; IND: [redacted]
Pending NDA 21-017 for a Humalog® 25%-75% mix similar to this application.

Drug Class: Insulin analog, recombinant human protein.

Indication: Treatment of hyperglycemia.

Clinical formulation:

Insulin Lispro Low and Mid Mixtures, 100 U/mL, 10 mL Vials and 3.0 mL Cartridges

	QUANTITY/mL LOW MIXTURE	QUANTITY/mL MID MIXTURE
Active ingredient:		
Lys-Pro Insulin (Insulin Lispro)	100 U	100 U
Other Ingredients:		
Dibasic Sodium Phosphate, USP	3.78 mg	3.78 mg
Glycerin, USP	16.00 mg	16.00 mg
Phenol, USP		
Metacresol, USP		
Protamine Sulfate, USP	0.28 mg	0.19 mg
Zinc Oxide, USP	q.s. for content of 0.025 mg Zn ⁺⁺ content	q.s. for content of 0.0305 mg Zn ⁺⁺ content
Hydrochloric Acid Solution 10%	qs	qs
Sodium Hydroxide Solution 10%	qs	qs
Water for Injection, USP		

Route of administration: Injectable, SC

Proposed clinical protocol or Use: As a rapid acting insulin analog for administration 15 minutes prior to a meal. This is described as a Lispro low mixture and Lispro mid mixture which vary slightly in contents of protamine sulfate, metacresol, phenol and zinc oxide.

Disclaimer – use of sponsor's material: Sponsor data tables are reproduced in this report.

INTRODUCTION AND DRUG HISTORY: The active ingredient of Humalog® was approved June 14, 1996. This is an analog of human insulin in which the natural sequence of proline and lysine in positions B28 and B29 have been reversed. Upon injection, the [redacted] of insulin lispro dissociates into monomer form more rapidly than human insulin. Thus, lispro insulin is marketed as a rapid-acting insulin. The present submission provides for new formulations of this product to provide a sustained release preparation, which is analogous to human insulin NPH and provides a longer action profile. Three formulations have been studied clinically referred to as Insulin Lispro Low, Mid and [redacted] mixtures which have the ratios of insulin lispro: NPL of 1:3, 1:1 and [redacted] respectively. It is expected that the Low and Mid mixtures would provide an intermediate-acting plasma insulin profile similar to those provided by human regular/NPH mixtures. In addition, a better postprandial glucose control is expected as a result of the rapid action of the lispro component. Investigational formulations differed slightly from the commercial formulations in quantities of protamine sulfate, metacresol and [redacted] phenol, each of which are slightly increased in the Commercial formulation, but within safe limits for the use of these inactive ingredients. The primary difference of this product compared to the approved Lispro product is that of the time-action profile. Given the extensive preclinical work done for the original NDA 20-563, limited preclinical studies have been provided in this NDA. The primary concerns with this product are the timing and effectiveness in the clinical population as well as the potential for antigenicity. Pivotal studies to determine the activity profile have been done in humans. The toxicity profile of most insulin products relates to the limitations of dosing due to severe hypoglycemia. Therefore, extensive preclinical studies of this product were not necessary.

Studies reviewed within this submission: Note: these are the same studies provided for NDA 21-017.

		Page #
I.	Nonclinical Pharmacology Report 1: Comparison of Insulin Lispro Protamine in Suspension (NPL) with NPH Human insulin in Rabbit Blood Glucose-Lowering Tests	3
II.	Nonclinical Pharmacology Report 2: Comparative Dynamics of Neutral Protamine Lispro (NPL) and NPH Human Insulin in Dogs	4
III.	Toxicology Report 29: The Acute Toxicity of LY275585 Administered Subcutaneously to Fischer 344 Rats	5

Studies not reviewed within this submission: None.

APPEARS THIS WAY
ON ORIGINAL

PHARMACOLOGY:

General Comments: The purpose of the following studies was to compare the new Lispro Insulin formulations to approved similar insulin products of NPH Human Insulin. These studies were intended to determine whether the properties of insulin lispro are altered by the co-crystallization with protamine.

Study Title: Comparison of Insulin Lispro Protamine in Suspension (NPL) with NPH Human Insulin in Rabbit Blood Glucose-Lowering Tests

Study No: Nonclinical Study Report 1

Amendment #, Vol. #, and page #: Original NDA vol. 30 Page 15.

Conducting laboratory and location: Lilly Research Laboratories; Indianapolis, IN 46285

Date of study initiation: Studies listed as performed on September 22 and 23, 1993.

GLP compliance: Not stated.

QA- Report Yes () No (X)

METHODS:

Dosing: Subcutaneous dosing

species/strain: Rabbit

#/sex/group or time point: 20 or 8 (two experiments). Sex not specified.

age: not provided

weight: not provided

dosage groups in administered units: NPH and NPL insulin suspensions were tested in two separate experiments on consecutive days.

route, form, volume, and infusion rate: SC injections of 0.2 U/kg of Humulin N and two different NPL preparations of 0.2 U/kg.

Drug, lot#, radiolabel, and % purity: NPH lot 6NM76A; NPL lots 9-14-1 and 9-14-2.

Formulation/vehicle: Not specified. Probably similar to clinical preparations.

OBSERVATIONS AND TIMES: Blood glucose levels were taken on samples taken at time 0, 0.5, 1.0, 2.0, 4.0 and 6 h after injection.

RESULTS:

Table 1: Blood glucose levels (mg/mL) in rabbits following SC injection (0.2 U/kg) of Humulin N and two different NPL preparations (n=20)

TIME (h)	9/22/93 experiment (n=20)		9/23/93 experiment (n=8)	
	NPH	NPL	NPH	NPL
0	82.9	86.2	84.4	85.4
0.5	47.2	48.6	55.2	56.3
1	45.8	49.6	63.0	63.4
2	54.0	66.1	76.5	76.9
4	75.7	82.0	84.1	82.4
6	78.7	81.3	nd	nd

KEY STUDY FINDINGS:

The time-action profiles for lowering of blood glucose for NPH and NPL were similar.

Study Title: Comparative Dynamics of Neutral Protamine Lispro (NPL) and NPH Human Insulin in Dogs

Study No: Nonclinical Study Report 2

Amendment #, Vol. #, and page #: Original NDA vol. 30 Page 40.

Conducting laboratory and location: Lilly Research Laboratories; Indianapolis, IN 46285

Date of study initiation: Series of experiments conducted between December 3, 1993-April 8, 1994.

GLP compliance: Not stated.

QA- Report Yes () No (X)

METHODS:

Dosing: Subcutaneous dosing 0.5 U/kg

species/strain: Dog (conscious, fasted 18 h)

#/sex/group or time point: 6 mongrel dogs were used in these studies. Each received NPL and NPH on different occasions.

age: not provided

weight: 15-25 kg

dosage groups in administered units: NPH and NPL insulin suspensions were tested in several experiments at 0.5 U/kg. See tables for groups. There was a concurrent infusion of 20% glucose to maintain a basal fasting glucose rate (glucose clamp).

route, form, volume, and infusion rate: SC injections of 0.5 U/kg of Humulin N and NPL.

Drug, lot#, radiolabel, and % purity: NPH lot N1A52D; NPL lot 2NZ160LPP152.

Formulation/vehicle: Not specified. Probably similar to clinical preparations.

OBSERVATIONS AND TIMES: Blood samples were taken at various time points as follows:

5 minute intervals for 45 minutes (45 min)

every 10 minutes for 40 minutes (85 min)

every 15 minutes for 30 minutes (115 min)

every 20 minutes for 40 minutes (155 min)

every 25 minutes for 150 minutes (305 min)

every 30 minutes until the end of the study (at least 8 h).

Immunoreactive insulin (IRI) levels were determined using [redacted] which detect both human insulin and lispro.

RESULTS:

Kinetic parameters for NPL and NPH

Parameter	NPL	NPH
C_{max} (ng/mL)	2.61 ± 0.22	2.58 ± 0.36
T_{max} (min)	93 ± 22	145 ± 33
Insulin area (ng·min/mL)	810 ± 71	680 ± 77

Pharmacodynamic parameters for NPL and NPH

Parameter	NPL	NPH
R_{max} (mg/kg-min)	10.8 ± 1.2	13.2 ± 1.9
T_{Rmax} (min)	277 ± 58	265 ± 38
Total glucose infused (g/kg)	3.35 ± 0.41	3.8 ± 0.65

KEY STUDY FINDINGS:

1. Insulin lispro protamine suspension had a similar kinetic and dynamic responses to those of NPH.
2. There were no statistically significant differences between the glucose response curves for the two products.
3. The time at which maximum insulin/insulin lispro concentration was reached was slightly different in the two preparations. This did not lead to any significant alteration in the response of glucose requirements between the two products.
4. The glucose requirements for NPL appeared to plateau for ~ 4.5 h.

TOXICOLOGY:

Study Title: The Acute Toxicity of LY275585 Administered Subcutaneously to Fischer 344 Rats

Study No: Toxicology Report 29, Study R17194

Amendment #, Vol. #, and page #: Initial NDA vol. 30 Page 77.

Conducting laboratory and location: Lilly Research Laboratories; Indianapolis, IN 46285

Date of study initiation: May 19, 1994.

GLP compliance: Yes

QA- Report Yes () No (X)

METHODS:

Dosing: SC

species/strain: Fischer 344 rats (non-fasted).

#/sex/group or time point: 5/sex/group.

age: ~ 8-9 weeks.

weight: males: 190.5 ± 5.6 g, females: 139.8 ± 4.0 g

dosage groups in administered units: control and 10 U/kg groups, 1 ml/kg.

route, form, volume, and infusion rate: SC

Drug, lot#, radiolabel, and % purity: CT03280, 100 U/ml. Bulk lot 382EM3

Formulation/vehicle: formulation in Humulin® BR Diluent pH 7.3

OBSERVATIONS AND TIMES:

Clinical signs: 1 h intervals for the first 6 hours post dosing, then daily up to 2 weeks.

Body weights: weekly.

Gross pathology: Examination of all external body surfaced and orifices, and the thoracic and abdominal cavities and their viscera.

RESULTS:

Clinical signs: No treatment related signs.

Body weights: No treatment-related effects.

Gross pathology: No treatment-related effects.

KEY STUDY FINDINGS:

1. Animals were apparently not dosed to the limits to demonstrate hypoglycemia in clinical signs. No toxicological effects were noted in the parameters observed.

OVERALL SUMMARY AND EVALUATION:

Introduction: The active ingredient of Humalog® was approved June 14, 1996. This is an analog of human insulin in which the natural sequence of proline and lysine in positions B28 and B29 have been reversed. Upon injection, the [redacted] of insulin lispro dissociates into monomer form much more rapidly than human insulin. Thus, lispro insulin is marketed as a rapid-acting insulin. The present submission provides for new formulations of this product to provide a sustained release preparation, which is analogous to human insulin NPH and provides a longer action profile than the currently approved formulation. Three formulations have been studied clinically referred to as Insulin Lispro Low, Mid and [redacted] mixtures which have the ratios of insulin lispro: NPL of 1:3, 1:1 and [redacted] respectively. It is expected that the Low and Mid mixtures would provide an intermediate-acting plasma insulin profile similar to those provided by human regular/NPH mixtures. In addition, a better postprandial glucose control is expected as a result of the rapid action of the lispro component. Investigational formulations differed slightly from the commercial formulations in quantities of protamine sulfate, metacresol and [redacted] phenol, each of which are slightly increased in the Commercial formulation, but within safe limits for the use of these inactive ingredients. The primary difference of this product compared to the approved Lispro product is that of the time-action profile. Given the extensive preclinical work done for the original NDA 20-563, limited preclinical studies have been provided in this NDA. The primary concerns with this product is the timing and effectiveness in the clinical population and the potential for antigenicity. Pivotal studies to determine the activity profile have been done in humans. The toxicity profile of most insulin products relates to the limitations of dosing due to severe hypoglycemia. Therefore, extensive preclinical studies of this product were not necessary.

Safety Evaluation: The primary preclinical issue for this product is the time-action profile of activity. The systemic toxicity of lispro insulin has been well characterized and is, in general similar to native insulin. Assuming that the new mix is stable in a patient setting, there should be no unexpected toxicity with the proposed mixtures.

Conclusions: The preclinical studies provided by the sponsor indicate that the proposed mixtures appear to have the predicted prolonged activity. There should be no unexpected toxicity with these mixtures. The key data for determining approvability will come from the pivotal human trials to determine action profile and antigenicity in humans. From a pharmacology standpoint, this NDA supplement is APPROVED.

COMMUNICATION REVIEW:

Labeling Review (NDA): Preclinical sections of the label are identical to current labeling for Humalog®. Labeling is acceptable. No changes are required for the preclinical sections of the label.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATIONS:

Internal comments: AP

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

/S/ *2/22/99*

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: IND
HFD510
HFD510/Steigerwalt/JRhee
Review Code: AP

APPEARS THIS WAY
ON ORIGINAL