CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20928

Trade Name: GLUCAGON FOR INJECTION

Generic Name: rDNA ORIGIN

Sponsor: ELI LILLY AND COMPANY

Approval Date: 09/11/98

Indication(s): TREATMENT OF SEVERE HYPOGLYCEMIA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20928

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)				X
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20928

APPROVAL LETTER

NDA 20-928

Eli Lilly and Company
Attention: Jennifer Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Stotka:

Please refer to your new drug application (NDA) dated December 11, 1997, received December 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucagon (rDNA origin) for Injection.

We acknowledge receipt of your submissions dated January 6, 7, 8, 16, 23, 26, and 27, February 13, 16, and 23, March 18, April 13, May 4, June 8, 10, and 18, July 1, August 13, 18, and 20, and September 8 and 10, 1998. Your submission of June 8, 1998, extended the user fee goal date to September 12, 1998.

This new drug application provides for the use of Glucagon (rDNA origin) for Injection for (1) the treatment of severe hypoglycemia, and (2) use as a diagnostic aid in the radiologic examination of the stomach, duodenum, small bowel, and colon when diminished intestinal motility would be advantageous.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (physician package insert submitted September 10, 1998, patient package insert submitted September 8, 1998, and immediate container and carton labels submitted July 1, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-928." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated June 8 and August 18, 1998. These commitments, along with any completion dates agreed upon, are listed below.

Please submit data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

APPEARS THIS WAY
ON ORIGINAL

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20928

FINAL PRINTED LABELING

Marked-up Physician Package insert
(diskette submisison date: September 8, 1998)

INFORMATION FOR THE PHYSICIAN

PA #### AMP

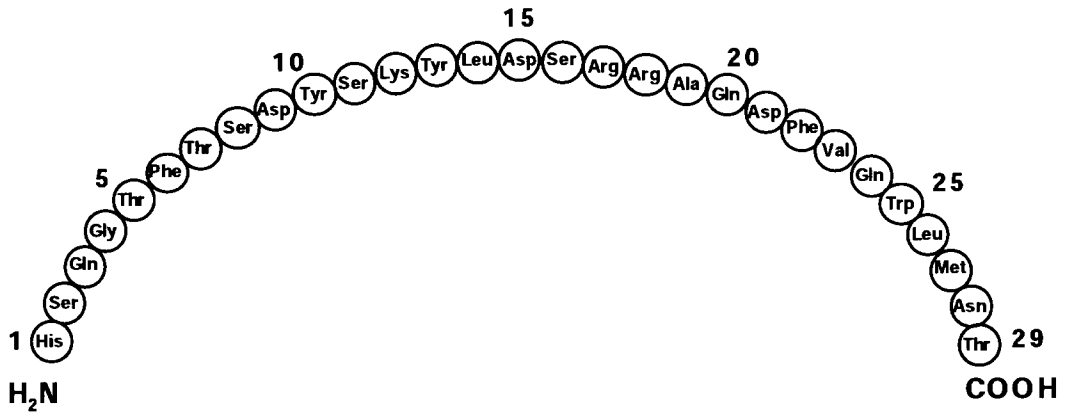
GLUCAGON FOR INJECTION (rDNA ORIGIN)

DESCRIPTION

Glucagon for Injection (rDNA origin) is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. Glucagon is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for glucagon.

Glucagon is a single-chain polypeptide that contains 29 amino acid residues and has a molecular weight of 3,483.

The empirical formula is $C_{153}H_{225}N_{43}O_{49}S$. The primary sequence of glucagon is shown below.



Crystalline glucagon is a white to off-white powder. It is relatively insoluble in water but is soluble at a pH of less than 3 or more than 9.5.

Glucagon is available for use intravenously, intramuscularly, or subcutaneously in a kit that contains a vial of sterile glucagon and a syringe of sterile diluent. The vial contains 1 mg (1 unit) of glucagon and 49 mg of lactose. Hydrochloric acid may have been added during manufacture to adjust the pH of the glucagon. One International Unit of glucagon is equivalent to 1 mg of glucagon.[1] The diluent syringe contains 12 mg/mL of glycerin, water for injection, and hydrochloric acid.

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CLINICAL PHARMACOLOGY

Glucagon increases blood glucose concentration and is used in the treatment of hypoglycemia. Glucagon acts only on liver glycogen, converting it to glucose.

Glucagon administered through a parenteral route relaxes smooth muscle of the stomach, duodenum, small bowel, and colon.

Pharmacokinetics

Glucagon has been studied following intramuscular, subcutaneous, and intravenous administration in adult volunteers. Administration of the intravenous glucagon showed dose proportionality of the pharmacokinetics between 0.25 and 2.0 mg. Calculations from a 1 mg dose showed a small volume of distribution (mean, 0.25 L/kg) and a moderate clearance (mean, 13.5 mL/min/kg). The half-life was short, ranging from 8 to 18 minutes.

Maximum plasma concentrations of 7.9 ng/mL were achieved approximately 20 minutes after subcutaneous administration (see Figure 1A). With intramuscular dosing, maximum plasma concentrations of 6.9 ng/mL were attained approximately 13 minutes after dosing.

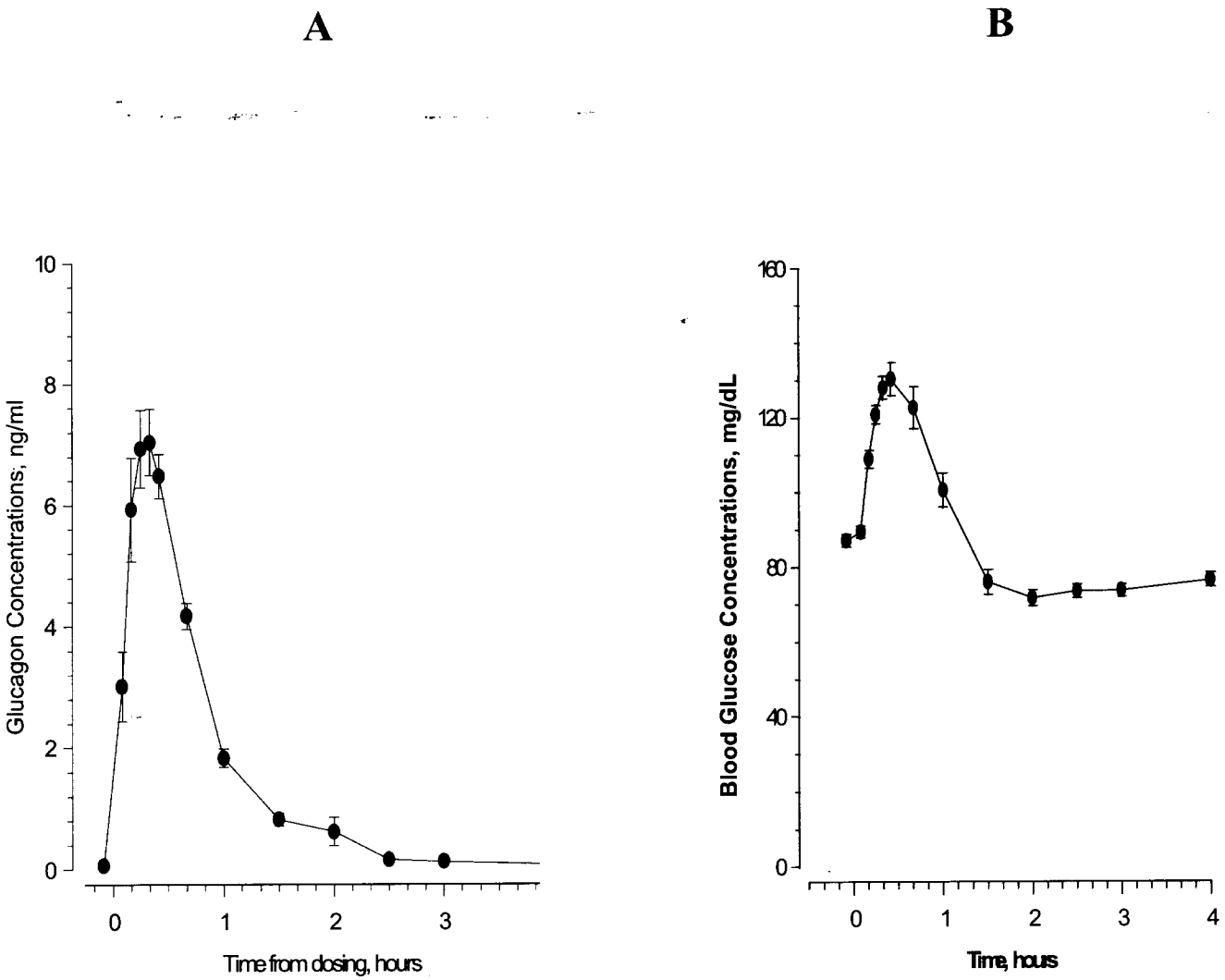
Glucagon is extensively degraded in liver, kidney, and plasma. Urinary excretion of intact glucagon has not been measured.

Pharmacodynamics

In a study of 25 volunteers, a subcutaneous dose of 1 mg glucagon resulted in a mean peak glucose concentration of 136 mg/dL 30 minutes after injection (see Figure 1B). Similarly, following intramuscular injection, the mean peak glucose level was 138 mg/dL, which occurred at 26 minutes after injection. No difference in maximum blood glucose concentration between animal-sourced and rDNA glucagon was observed after subcutaneous and intramuscular injection.

Figure 1

Mean (±SE) serum glucagon and blood glucose levels after subcutaneous injection of glucagon (1mg) in 25 normal volunteers



INDICATIONS AND USAGE

For the treatment of hypoglycemia:

Glucagon is indicated as a treatment for severe hypoglycemia.

Because patients with type 1 diabetes may have less of an increase in blood glucose levels compared with a stable type 2 patient, supplementary carbohydrate should be given as soon as possible, especially to a pediatric patient.

For use as a diagnostic aid:

Glucagon is indicated as a diagnostic aid in the radiologic examination of the stomach, duodenum, small bowel, and colon when diminished intestinal motility would be advantageous.

Glucagon is as effective for this examination as are the anticholinergic drugs. However, the addition of the anticholinergic agent may result in increased side effects.

CONTRAINDICATIONS

Glucagon is contraindicated in patients with known hypersensitivity to it or in patients with known pheochromocytoma.

WARNINGS

Glucagon should be administered cautiously to patients with a history suggestive of insulinoma, pheochromocytoma, or both. In patients with insulinoma, intravenous administration of glucagon may produce an initial increase in blood glucose; however, because of glucagon's hyperglycemic effect the insulinoma may release insulin and cause subsequent hypoglycemia. A patient developing symptoms of hypoglycemia after a dose of glucagon should be given glucose orally, intravenously, or by gavage, whichever is most appropriate.

Exogenous glucagon also stimulates the release of catecholamines. In the presence of pheochromocytoma, glucagon can cause the tumor to release catecholamines, which may result in a sudden and marked increase in blood pressure. If a patient develops a sudden increase in blood pressure, 5 to 10 mg of phentolamine mesylate may be administered intravenously in an attempt to control the blood pressure.

Generalized allergic reactions, including urticaria, respiratory distress, and hypotension, have been reported in patients who received glucagon by injection.

PRECAUTIONS

General--Glucagon is effective in treating hypoglycemia only if sufficient liver glycogen is present. Because glucagon is of little or no help in states of starvation, adrenal insufficiency, or chronic hypoglycemia, hypoglycemia in these conditions should be treated with glucose.

Information for Patients--Refer patients and family members to the attached Information for the User for instructions describing the method of preparing and injecting glucagon. Advise the patient and family members to become familiar with the technique of preparing glucagon

before an emergency arises. Instruct patients to use 1 mg (1 unit) for adults and 1/2 the adult dose (0.5 mg) [0.5 unit] for pediatric patients weighing less than 44 lb (20 kg).

Patients and family members should be informed of the following measures to prevent hypoglycemic reactions due to insulin:

1. Reasonable uniformity from day to day with regard to diet, insulin, and exercise.
2. Careful adjustment of the insulin program so that the type (or types) of insulin, dose, and time (or times) of administration are suited to the individual patient.
3. Frequent testing of the blood or urine for glucose so that a change in insulin requirements can be foreseen.
4. Routine carrying of sugar, candy, or other readily absorbable carbohydrate by the patient so that it may be taken at the first warning of an oncoming reaction.

To prevent severe hypoglycemia, patients and family members should be informed of the symptoms of mild hypoglycemia and how to treat it appropriately.

Family members should be informed to arouse the patient as quickly as possible because prolonged hypoglycemia may result in damage to the central nervous system. Glucagon or intravenous glucose should awaken the patient sufficiently so that oral carbohydrates may be taken.

Patients should be advised to inform their physician when hypoglycemic reactions occur so that the treatment regimen may be adjusted if necessary.

Laboratory Tests--Blood glucose determinations should be obtained to follow the patient with hypoglycemia until patient is asymptomatic.

Carcinogenesis, Mutagenesis, Impairment of Fertility --Because glucagon is usually given in a single dose and has a very short half-life, no studies have been done regarding carcinogenesis. In a series of studies examining effects on the bacterial mutagenesis (Ames) assay, it was determined that an increase in colony counts was related to technical difficulties in running this assay with peptides and was not due to mutagenic activities of the glucagon.

Reproduction studies have been performed in rats at doses up to 2 mg/kg glucagon administered two times a day (up to 40 times the human dose based on body surface area, mg/m^2) and have revealed no evidence of impaired fertility.

Pregnancy--Pregnancy Category B--Reproduction studies have not been performed with recombinant glucagon. However, studies with animal-sourced glucagon were performed in rats at doses up to 2 mg/kg glucagon administered two times a day (up to 40 times the human dose based on body surface area, mg/m^2), and have revealed no evidence of impaired fertility or harm to the fetus due to glucagon. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers--It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when glucagon is administered to a nursing woman. If the drug is excreted in human milk during its short half-life, it will be hydrolyzed and absorbed like any other polypeptide. Glucagon is not active when taken orally because it is destroyed in the gastrointestinal tract before it can be absorbed.

Pediatric Use--For the treatment of hypoglycemia: The use of glucagon in pediatric patients has been reported to be safe and effective.[2-6]

For use as a diagnostic aid: Effectiveness has not been established in pediatric patients.

ADVERSE REACTIONS

Severe adverse reactions are very rare, although nausea and vomiting may occur occasionally. These reactions may also occur with hypoglycemia. Generalized allergic reactions have been reported (*see* WARNINGS). In a three month controlled study of 75 volunteers comparing animal-sourced glucagon with glucagon manufactured through rDNA technology, no glucagon-specific antibodies were detected in either treatment group.

OVERDOSAGE

Signs and Symptoms-- If overdosage occurs, nausea, vomiting, gastric hypotonicity, and diarrhea would be expected without causing consequential toxicity.

Intravenous administration of glucagon has been shown to have positive inotropic and chronotropic effects. A transient increase in both blood pressure and pulse rate may occur following the administration of glucagon. Patients taking ß-blockers might be expected to have a greater increase in both pulse and blood pressure, an increase of which will be transient because of glucagon's short half-life. The increase in blood pressure and pulse rate may require therapy in patients with pheochromocytoma or coronary artery disease.

When glucagon was given in large doses to patients with cardiac disease, investigators reported a positive inotropic effect. These investigators administered glucagon in doses of 0.5 to 16 mg/hour by continuous infusion for periods of 5 to 166 hours. Total doses ranged from 25 to 996 mg, and a 21-month-old infant received approximately 8.25 mg in 165 hours. Side effects included nausea, vomiting, and decreasing serum potassium concentration. Serum potassium concentration could be maintained within normal limits with supplemental potassium.

The intravenous median lethal dose for glucagon in mice and rats is approximately 300 mg/kg and 38.6 mg/kg, respectively.

Because glucagon is a polypeptide, it would be rapidly destroyed in the gastrointestinal tract if it were to be accidentally ingested.

Treatment--To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

In view of the extremely short half-life of glucagon and its prompt destruction and excretion, the treatment of overdosage is symptomatic, primarily for nausea, vomiting, and possible hypokalemia.

If the patient develops a dramatic increase in blood pressure, 5 to 10 mg of phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of glucagon; it is extremely unlikely that one of these procedures would ever be indicated.

DOSAGE AND ADMINISTRATION

General Instructions for Use:

- The diluent is provided for use only in the preparation of glucagon for parenteral injection and for no other use.
- Glucagon should not be used at concentrations greater than 1 mg/mL (1 unit/mL).
- Reconstituted glucagon should be used immediately. **Discard any unused portion.**
- Reconstituted glucagon solutions should be used only if they are clear and of a water-like consistency.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Directions for Treatment of Severe Hypoglycemia:

Severe hypoglycemia should be treated initially with intravenous glucose, if possible .

1. If parenteral glucose can not be used, dissolve the lyophilized glucagon using the accompanying diluting solution and use immediately.
2. For adults and for pediatric patients weighing more than 44 lb (20 kg), give 1 mg (1 unit) by subcutaneous, intramuscular, or intravenous injection.
3. For pediatric patients weighing less than 44 lb (20 kg), give 0.5 mg (0.5 unit) or a dose equivalent to 20-30 µg/kg.[2-6]
4. **Discard any unused portion.**
5. An unconscious patient will usually awaken within 15 minutes following the glucagon injection. If the response is delayed, there is no contraindication to the administration of an additional dose of glucagon; however, in view of the deleterious effects of cerebral hypoglycemia, emergency aid should be sought so that parenteral glucose can be given.
6. After the patient responds, supplemental carbohydrate should be given to restore liver glycogen and to prevent secondary hypoglycemia.

Directions for Use as a Diagnostic Aid:

Dissolve the lyophilized glucagon using the accompanying diluting solution and use immediately. **Discard any unused portion.**

The doses in the following table may be administered for relaxation of the stomach, duodenum, and small bowel, depending on the onset and duration of effect required for the examination. Since the stomach is less sensitive to the effect of glucagon, 0.5 mg (0.5 units) IV or 2 mg (2 units) IM are recommended.

Dose	Route of Administration	Time of Onset of Action	Approximate Duration of Effect

0.25-0.5 mg (0.25-0.5 units)	IV	1 minute	9-17 minutes
1 mg (1 unit)	IM	8-10 minutes	12-27 minutes
2 mg*(2 units)	IV	1 minute	22-25 minutes
2 mg*(2 units)	IM	4-7 minutes	21-32 minutes

*Administration of 2 mg (2 units) doses produces a higher incidence of nausea and vomiting than do lower doses.

For examination of the colon, it is recommended that a 2 mg (2 units) dose be administered intramuscularly approximately 10 minutes prior to the procedure. Colon relaxation and reduction of patient discomfort may allow the radiologist to perform a more satisfactory examination.

HOW SUPPLIED

Glucagon Emergency Kit for Low Blood Sugar (Glucagon for Injection [rDNA origin]) (MS8031):

1 mg (1 unit)--(VL7529), with 1 mL of diluting solution (Hyporet ®* HY7530) (1s) NDC 0002-8031-01

Glucagon Diagnostic Kit (Glucagon for Injection [rDNA origin]) (MS8085):

1 mg (1 unit)--(VL7529), with 1 mL of diluting solution (Hyporet ®* HY7530) (1s) NDC 0002-8085-01 (available in US market only).

*Hyporet® (disposable syringe, Lilly).

***Stability and Storage*:**

Before Reconstitution--Vials of Glucagon, as well as the Diluting Solution for Glucagon , may be stored at controlled room temperature 20 ° to 25°C (68° to 77°F)[see USP].

The USP defines controlled room temperature by the following: A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

After Reconstitution--Glucagon for Injection (rDNA origin) should be used immediately. **Discard any unused portion.**

REFERENCES

1. *Drug Information for the Health Care Professional*. 18th ed. Rockville, Maryland: The United States Pharmacopeial Convention, Inc; 1998; I:1512 .

2. Gibbs et al: Use of glucagon to terminate insulin reactions in diabetic children. *Nebr Med J* 1958;43:56-57.

3. Cornblath M, et al: Studies of carbohydrate metabolism in the newborn: Effect of glucagon on concentration of sugar in capillary blood of newborn infant. *Pediatrics* 1958;21:885-892.

4. Carson MJ, Koch R: Clinical studies with glucagon in children. *J Pediatr* 1955;47:161-170.

5. Shipp JC, et al: Treatment of insulin hypoglycemia in diabetic campers. *Diabetes* 1964;13:645-648.

6. Aman J, Wranne L: Hypoglycemia in childhood diabetes II: Effect of subcutaneous or intramuscular injection of different doses of glucagon. *Acta Pediatr Scand* 1988;77:548-553.

Literature issued ~~June 10~~, 1998

Eli Lilly and Company
Indianapolis, IN 46285, USA

PA #### AMPX

PRINTED IN USA

Diskette submission date: 9/8/98

PA #### AMP

INFORMATION FOR THE USER

GLUCAGON FOR INJECTION (rDNA ORIGIN)

BECOME FAMILIAR WITH THE FOLLOWING INSTRUCTIONS BEFORE AN EMERGENCY ARISES. DO NOT USE THIS KIT AFTER DATE STAMPED ON THE BOTTLE LABEL. IF YOU HAVE QUESTIONS CONCERNING THE USE OF THIS PRODUCT, CONSULT A DOCTOR, NURSE OR PHARMACIST.

Make sure that your relatives or close friends know that if you become unconscious, medical assistance must always be sought. Glucagon may have been prescribed so that members of your household can give the injection if you become hypoglycemic and are unable to take sugar by mouth. If you are unconscious, glucagon can be given while awaiting medical assistance.

IMPORTANT

- Act quickly. Prolonged unconsciousness may be harmful.
- These simple instructions will help you give glucagon successfully.
- Turn patient on his/her side to prevent patient from choking.
- The contents of the syringe are inactive. You must mix the contents of the syringe with the glucagon in the accompanying bottle before giving injection. (See DIRECTIONS FOR USE below.)
- Do not prepare Glucagon for Injection until you are ready to use it.

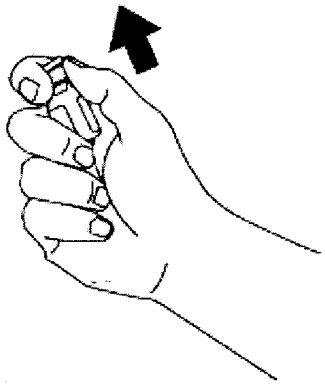
WARNING: THE PATIENT MAY BE IN A COMA FROM SEVERE HYPERGLYCEMIA (HIGH BLOOD GLUCOSE) RATHER THAN HYPOGLYCEMIA. IN SUCH A CASE, THE PATIENT WILL **NOT** RESPOND TO GLUCAGON AND REQUIRES IMMEDIATE MEDICAL ATTENTION.

INDICATIONS FOR USE

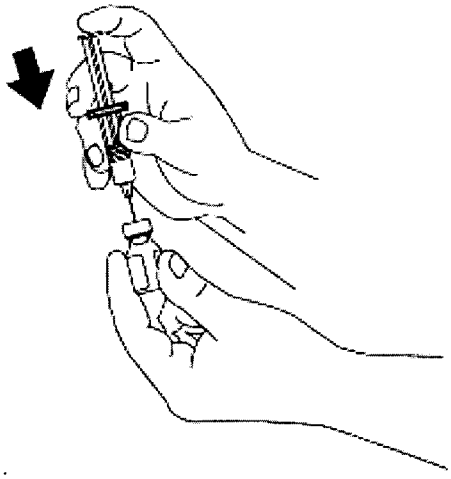
Use glucagon to treat insulin coma or insulin reaction resulting from severe hypoglycemia (low blood sugar). Symptoms of severe hypoglycemia include disorientation, unconsciousness, and seizures or convulsions. Give glucagon if (1) the patient is unconscious, (2) the patient is unable to eat sugar or a sugar-sweetened product, (3) the patient is having a seizure, or (4) repeated administration of sugar or a sugar-sweetened product such as a regular soft drink or fruit juice does not improve the patient's condition. Milder cases of hypoglycemia should be treated promptly by eating sugar or a sugar-sweetened product. (See INFORMATION ON HYPOGLYCEMIA below for more information on the symptoms of hypoglycemia.) Glucagon is not active when taken orally.

DIRECTIONS FOR USE
TO PREPARE GLUCAGON FOR INJECTION

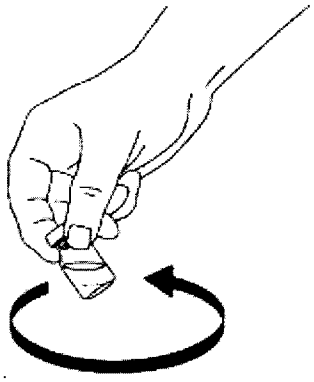
1. Remove the flip-off seal from the bottle of glucagon. Wipe rubber stopper on bottle with alcohol swab.



2. Remove the needle protector from the syringe, and inject the entire contents of the syringe into the bottle of glucagon. DO NOT REMOVE THE PLASTIC CLIP FROM THE SYRINGE. Remove syringe from the bottle.

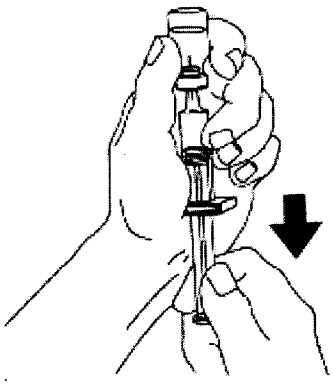


3. Swirl bottle gently until glucagon dissolves completely. GLUCAGON SHOULD NOT BE USED UNLESS THE SOLUTION IS CLEAR AND OF A WATER-LIKE CONSISTENCY.



TO INJECT GLUCAGON
Use Same Technique as for Injecting Insulin

4. Using the same syringe, hold bottle upside down and, making sure the needle tip remains in solution, gently withdraw all of the solution (1 mg mark on syringe) from bottle. The plastic clip on the syringe will prevent the rubber stopper from being pulled out of the syringe; however, if the plastic plunger rod separates from the rubber stopper, simply reinsert the rod by turning it clockwise. The usual adult dose is 1 mg (1 unit). For children weighing less than 44 lb (20 kg), give 1/2 adult dose (0.5 mg). For children, withdraw 1/2 of the solution from the bottle (0.5 mg mark on syringe). DISCARD UNUSED PORTION.



USING THE FOLLOWING DIRECTIONS, INJECT GLUCAGON IMMEDIATELY AFTER MIXING.

5. Cleanse injection site on buttock, arm, or thigh with alcohol swab.

6. Insert the needle into the loose tissue under the cleansed injection site, and inject all (or ½ for children weighing less than 44 lb) of the glucagon solution. THERE IS NO DANGER OF OVERDOSE. Apply light pressure at the injection site, and withdraw the needle. Press an alcohol swab against the injection site.

7. Turn the patient on his/her side. When an unconscious person awakens, he/she may vomit. Turning the patient on his/her side will prevent him/her from choking.

8. FEED THE PATIENT AS SOON AS HE/SHE AWAKENS AND IS AB LE TO SWALLOW. Give the patient a fast-acting source of sugar (such as a regular soft drink or fruit juice) and a long-acting source of sugar (such as crackers and cheese or a meat sandwich). If the patient does not awaken within 15 minutes, give another dose of glucagon and INFORM A DOCTOR OR EMERGENCY SERVICES IMMEDIATELY.

9. Even if the glucagon revives the patient, his/her doctor should be promptly notified. A doctor should be notified whenever severe hypoglycemic reactions occur.

INFORMATION ON HYPOGLYCEMIA

Early symptoms of hypoglycemia (low blood glucose) include:

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- abnormal behavior
- unsteady movement
- personality changes

If not treated, the patient may progress to severe hypoglycemia that can include:

- disorientation
- unconsciousness
- seizures
- death

The occurrence of early symptoms calls for prompt and, if necessary, repeated administration of some form of carbohydrate. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. The prompt treatment of mild hypoglycemic symptoms can prevent severe hypoglycemic reactions. If the patient does not improve or if administration of carbohydrate is impossible, glucagon should be given or the patient should be treated with intravenous glucose at a medical facility. Glucagon, a naturally occurring substance produced by the pancreas, is helpful because it enables the patient to produce his/her own blood glucose to correct the hypoglycemia.

POSSIBLE PROBLEMS WITH GLUCAGON TREATMENT

Severe side effects are very rare, although nausea and vomiting may occur occasionally. A few people may be allergic to glucagon or to one of the inactive ingredients in glucagon, or may experience rapid heart beat for a short while.

If you experience any other reactions which are likely to have been caused by glucagon, please contact your doctor.

STORAGE

Before dissolving glucagon with diluting solution—Store the kit at controlled ~~at~~ room temperature ~~between~~ 20° to 25°C (68° to 77°F).

After dissolving glucagon with diluting solution—Should be used immediately. **Discard any unused portion.** Solutions should be clear and of a water-like consistency at time of use.

Literature issued ~~July 1~~, 1998

Eli Lilly and Company
Indianapolis, IN 46285, USA

PA #### AMP

PRINTED IN USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20928

MEDICAL REVIEW(S)

FEB 6 1998

New Drug Application

NDA 20,928

Glucagon for injection (rDNA origin)

submitted by Eli Lilly letter date December 11, 1997

stamp date December 12, 1997

documents reviewed: NDA 20,928 submitted December 11, 1997

related product: GlucaGen (Glucagon rDNA) Novo-Nordisk, NDA 29-918

Medical Officer's Review
February 4 , 1998

APPEARS THIS WAY
ON ORIGINAL

CC: Orig NDA
HFD-510/Div File
HFD-510/Misbin/Berlin/H Rhee
HFD-870/Shore
HFD-510/J Rhee

APPEARS THIS WAY
ON ORIGINAL

INTRODUCTION

This application is for a recombinant glucagon which has the same chemical structure as the animal-sourced glucagon which is currently marketed by Eli Lilly. In consultation with Lilly, FDA agreed that approval of this NDA could be based on a demonstration of bioequivalence with the existing product provided that the new product was not associated with any safety risks which were clinically important. It was also agreed that Lilly would submit antibody and efficacy data from a repeated injection study to test for tachyphylaxis and antibody formation.

Justification for priority review:

At present, the only glucagon available in the United States is animal-sourced glucagon produced by Eli Lilly. The primary advantage of rGlucagon over animal-sourced glucagon is that it is not dependent on the availability of animal tissue. Since most insulin used today is recombinant, there is little incentive for Lilly to maintain a stable supply of animal pancreas.

DEMONSTRATION OF EFFICACY:

Demonstration of efficacy rests on study GFAB which is a bioequivalence study conducted in healthy volunteers comparing Glucagon rDNA to the currently marketed animal glucagon. This study consists of two parts:

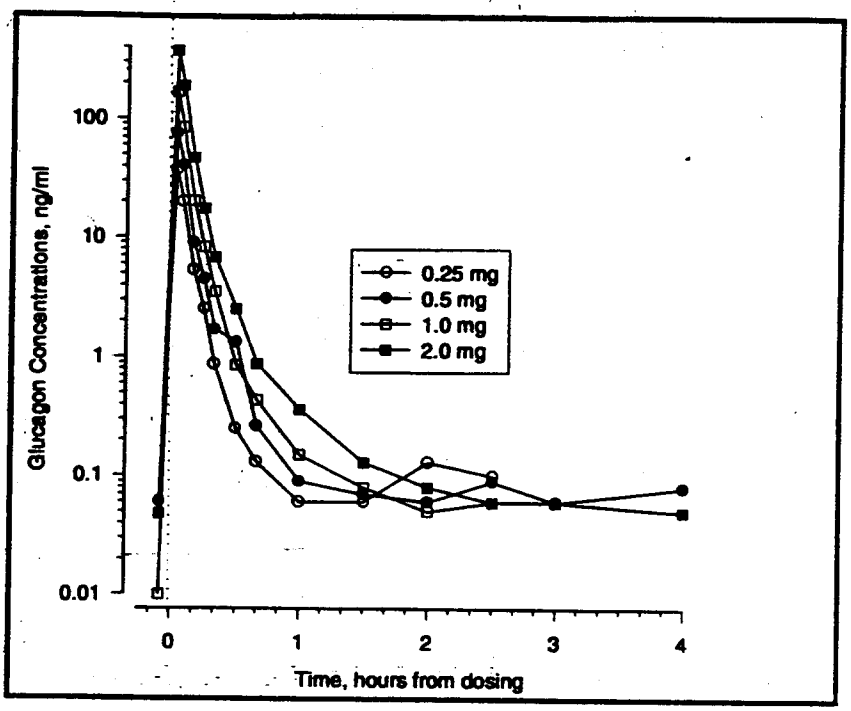
Part 1 is a dose-ranging study using rGlucagon (pH 2.8) given intravenously in doses of 0.25 to 2.0 mg to 12 healthy male and female volunteers. Plasma glucagon levels and corresponding glucose levesl are shown in the figures on the next page. C max, AUC, and t ½ are shown below:

r Glucagon dose, iv	t ½ hours	AUC ng.hr/ml	C max ng/ml
0.25mg	0.128	4.07	37
0.5mg	0.153	8.48	78
1.0mg	0.222	17.9	171
2.0mg	0.299	37.7	368

There is excellent proportionality between the dose administered and the C max and AUC. The half life was about 7 minutes at the 0.25 mg dose and 18 minutes at 2.0 mg dose, with the difference in half life probably reflecting partial saturation of glucagon clearance at the higher doses. Despite the wide differences in glucagon concentration, there were no differences among the doses with respect to pharmacodynamic measures as shown below:

r Glucagon dose, iv	BG max, mg/dl	TBG max, hours	AUCmg.hr/dl
0.25mg	131	0.34	137
0.50mg	138	0.35	137
1.0mg	132	0.36	101
2.0mg	129	0.35	123

These results reflect the fact that the maximal effective concentration of glucagon was exceeded even with the lowest dose. In the physiological setting a value of about 0.3 ng/ml would be a peak increment in response to potent glucagon secretagogs like arginine. That the prolonged hyperglucagonemia observed at the 2.0 mg dose (see figures) does not not cause more prolonged hyperglycemia than glucagon levels achieved at 0.25 mg illustrates glucagon's status as a bolus hormone. It works quickly and is dissipated quickly. From a clinical point of view, this means that the exact amount of hormone which is delivered is not critical and that the most important PK parameter is C max.



Mean Plasma Glucagon Concentrations following IV administration of rGlucagon. N≥10 for all curves.

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ON ORIGINAL

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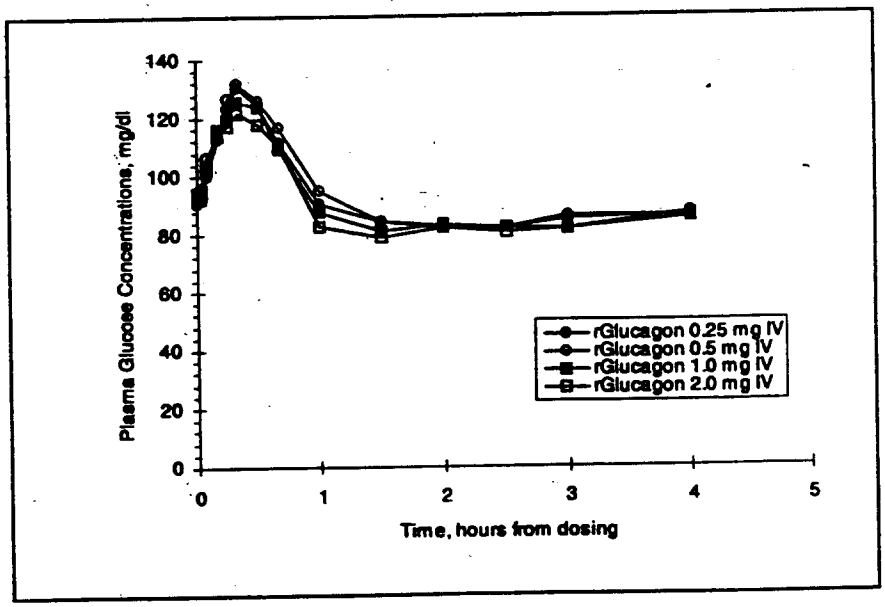

Mean Blood Glucose Concentration vs. Time Curves, All Intravenous Treatments (Part I). N≥10. ●=0.25 mg, ○=0.5 mg, ■=1.0 mg, □=2.0 mg

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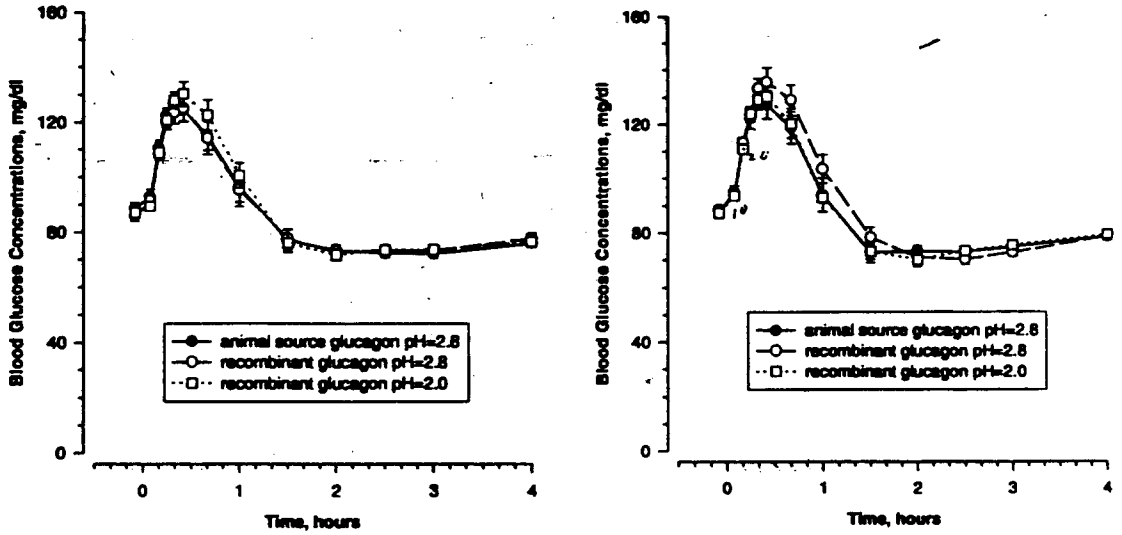
Part 2 is a comparison of r Glucagon (pH 2.0 and 2.8) with animal glucagon pH 2.8 given by sc or im injection to 29 healthy male and female volunteers. Glucagon and glucose levels and PK/PD measurements are shown in the following figures and tables. In general it can be seen that the highest glucagon levels were oberved with rGlucagon pH 2.8, followed by animal glucagon and rGlucagon pH 2.0. While the highest glucagon blood levels were obtained after injection of rGlucagon pH 2.8, the reduction of the pH to 2.0 may be justified on the grounds that the reconsitituted product will be more stabile.



Mean Blood Glucose Concentration versus Time Curves, All Treatments. Left panel shows subcutaneous (SC) administrations; right panel shows intramuscular (IM) administrations. Bars indicate standard errors. N≥25. ●=animal-source glucagon pH 2.8,○ =rGlucagon pH 2.8, □=rGlucagon pH 2.0.

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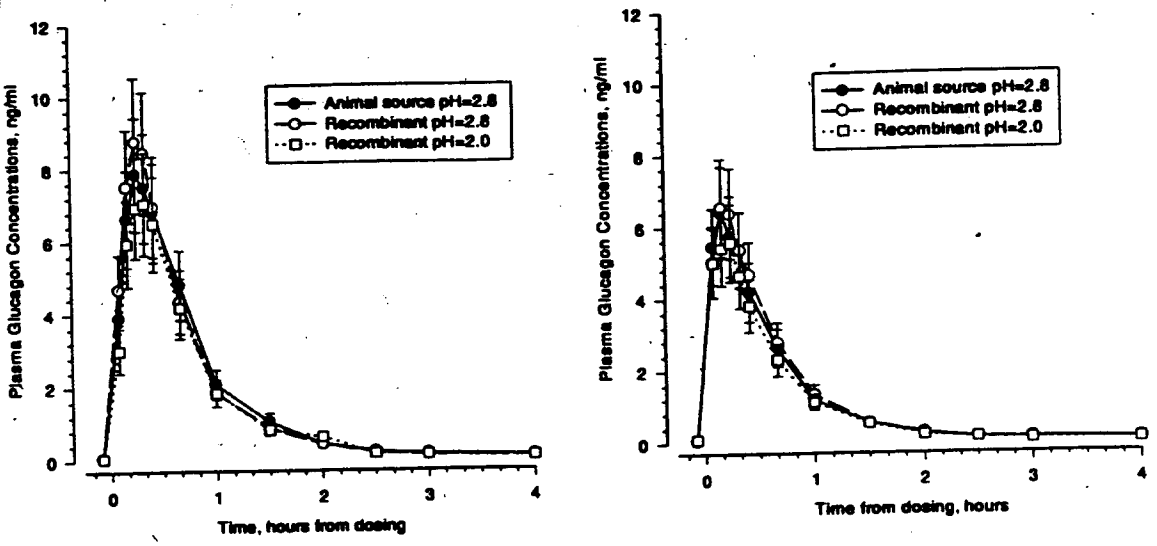
ON ORIGINAL



Mean Plasma Glucagon Concentration versus Time Curves, All Treatments, Part II. Left panel shows subcutaneous (SC) administrations; right panel shows intramuscular (IM) administrations. Bars indicate standard errors. N≥25. ●=animal-source pH 2.8, O=rGlucagon pH 2.8, □=rGlucagon pH 2.0.

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Mean (±SD) Pharmacokinetic Parameters and Bioequivalence Assessments, Subcutaneous Administrations

		$t_{½}$, hours	C_{max}, ng/ml	t_{max}, hours	$AUC_{(0-t)}$, ng•hr/ml	$AUC_{(0-inf)}$, ng•hr/ml
Animal-source pH=2.8	(A)	0.488 ± 0.166	9.12 ± 5.11	0.33 ± 0.10	6.57 ± 2.29	6.63 ± 2.30
Recombinant pH=2.8	(B)	0.451 ± 0.146	10.0 ± 3.65	0.27 ± 0.11	6.43 ± 2.15	6.47 ± 2.15
Recombinant pH=2.0	(C)	0.461 ± 0.166	7.94 ± 3.83	0.35 ± 0.098	5.82 ± 1.61	5.87 ± 1.62
			90 % CI		**90 % CI**	**90 % CI**
B vs. A[a]			102-126		91.4-109	91.2-109
C vs. A[a]			79.1-97.8		82.4-98.2	82.4-98.1
C vs. B[a]			69.8-86.3		82.5-98.4	82.8-98.5

Mean (±SD) Pharmacokinetic Parameters and Bioequivalence Assessments, Intramuscular Administrations

		$t_{½}$, hours	C_{max}, ng/ml	t_{max}, hours	$AUC_{(0-t)}$, ng•hr/ml	$AUC_{(0-inf)}$, ng•hr/ml
Animal-source pH=2.8	(D)	0.414 ± 0.147	7.36 ± 2.51	0.22 ± 0.10	4.31 ± 1.36	4.36 ± 1.38
Recombinant pH=2.8	(E)	0.382 ± 0.100	7.81 ± 3.57	0.21 ± 0.11	4.62 ± 1.86	4.67 ± 1.87
Recombinant pH=2.0	(F)	0.364 ± 0.141	6.90 ± 2.64	0.22 ± 0.095	3.92 ± 1.48	3.97 ± 1.49
			90 % CI		**90 % CI**	**90 % CI**
D vs. E[a]			93.6-115		97.1-115	97.4-116
D vs. F[a]			85.2-105		83.6-99.5	83.8-99.6
E vs. F[a]			82.1-101		78.9-93.9	79.1-93.9

[a]Comparisons reflect bioequivalence assessments based on log-transformed parameters. The specified range for any given parameter is the 90% confidence interval (90% CI) of the comparative ratios. If the interval falls between a range of 80% to 125%, it meets the standard bioequivalence criteria.

Although the Sponsor did not perform this comparison, it appears that higher glucagon levels were achieved following subcutaneous administration than following intramuscular administration. However, blood glucose levels and PD parameters were all the same. Indeed, it is worthy of note that the BG max of 132-143 mg/dl observed after im and sc administration is virtual identical to the BG max of 129-138 mg.dl observed after iv adminstration described earlier although glucagon concentrations given iv were much higher. Based on the data from intravenous adminstration, it appears to take about 0.3 hours for glucagon to exert its full effect (TBG max - T max = 0.35 - 0.05 hrs) The maximal glucose response is delayed after sc or im adminstration compared to iv because of time required for glucagon absorption. But this delay is small. TBG max is about 0.48 hours after sc glucagon and 0.42 hours after im glucagon compared to 0.35 hours after iv glucagon. That the time for the maximal glucose response after either sc or im administration are so close to that for iv probably means that glucodynamic activity is maximal after im or sc administration well before the maximal hormone concentration is achieved. This provides further evidence that small differences in C max after a 1mg injection are not important becasue the amount which is given is greatly in excess of what is required.

route of administration of glucagon	T max, time to max (Glucagon), hrs	TBG max time to max (Glucose), hours
intravenous, rGluc pH 2.0	0.05	0.35
subcutan., mean of 3 preps	0.46	0.48
intramuscular, mean of 3	0.39	0.42

With respect to PK, the pertinent comparison is between the already marketed animal-sourced glucagon pH 2.8 and the to be- marketed rGlucagon pH 2.0. Bioequivalence is achieved for im administration with C max ratio of (mean C max= 6.9 ng/ml for rGlucagon and 7.36 for animal glucagon). Bioequivalence is almost achieved for sc administration with a C max ratio of (mean C max 7.94 ng/ml with rGlucagon and 9.12 for animal glucagon). For the reasons discussed above, it is not of concern that C max is slightly lower with r Glucagon than with animal- sourced glucagon.

There were no serious adverse events reported during the PK study. Dizziness and nausea were reported by a few patients but no consistent differences was observed between the preparations or routes of administration. One patient withdrew from the study because of nausea, dizziness and pallor after animal -sourced glucagon.

SAFETY:

As noted above, there were no major or unexpected adverse events during the PK study.

The major safety concern has been related to antibody production after repeated injection, directed either to glucagon itself or to E coli peptide. Study GFAB consisted of three IM injections given three weeks apart of either rGlucagon (n=50) or animal-sourced glucagon n=25) to healthy volunteers. As shown in the table, dizziness, nausea, vomiting, headache and vasodilation were reported with both preparations, but there was no clear difference between the two. The most common adverse event, nausea, was reported 27 times by 14/50 subjects who received rGlucagon and 10 times by 7/25 subjects who received animal-sourced glucagon. Three subjects withdrew from the study due to adverse events. All three had received r Glucagon. One reported throat tightness(the form says "bitter taste in mouth") 2 hours after the second injection. One had a rash 31 hours after injection and one had rectal bleeding due to colon cancer four days after injection. No antiglucagon antibodies were detected with either preparation. Also, no net change in antibody titer to E coli peptide was observed in either group.

Drug Related Adverse Events in Study GFAB

Event Class Term	Relationship to Study Drug	rGlucagon N=50 # Events	rGlucagon N=50 # Subjects	Glucagon N=25 # Events	Glucagon N=25 # Subjects
ABDOMINAL PAIN	Possibly	1	1	0	0
ASTHENIA	Possibly	2	2	1	1
	Probably	1	1	2	2
BACK PAIN	Possibly	0	0	1	1
CONFUSION	Possibly	1	1	0	0
DIARRHEA	Possibly	1	1	0	0
DIZZINESS	Possibly	1	1	0	0
	Probably	20	11	14	7
DRY MOUTH	Possibly	1	1	0	0
DYSPEPSIA	Probably	1	1	0	0
HEADACHE	Possibly	6	5	6	4
	Probably	7	6	4	4
NAUSEA	Possibly	3	1	0	0
	Probably	27	14	10	7
NERVOUSNESS	Possibly	1	1	0	0
	Probably	0	0	1	1
PAIN	Possibly	3	1	0	0
PALPITATION	Probably	0	0	2	2
PHARYNGITIS	Possibly	1	1	0	0
PRURITUS	Possibly	6	1	0	0
RASH	Possibly	6	1	0	0
SWEATING	Probably	1	1	1	1
SYNCOPE	Probably	1	1	1	1
TASTE PERVERSION	Possibly	1	1	0	0
THIRST	Possibly	1	1	1	1
VASODILATATION	Possibly	1	1	0	0
	Probably	2	2	5	5
VOMITING	Possibly	1	1	0	0
	Probably	10	7	2	2

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LABELING ISSUES:

Pharmacodynamics:

The statement "no difference in glucodynamic activity between animnal-sourced and r Glucagon was observed" should be changed. The study would not have detected such a difference had it existed. I would suggest showing a figure with plasma glucagon and glucose levels for the two preparations of interest. The new figure could replace the present figure 1 which is itself not very informative.

APPEARS THIS WAY
ON ORIGINAL

Dosage and Adminstration:

I do not understand the statement under paragraph #5 " the physician MUST consider use of parenteral glucose." Is it intendcd that the use of glucose be considered in lieu of glucagon or after glucagon has been given and the patient remains unresponsive? Or is the point that physicians must consider parenteral glucose but other people (relatives for instance) can give glucagon? The intended meaning is unclear and the statement should be reworded. Also, a 15 minute response-time is reasonable for sc or im glucagon but iv glucagon has a more rapid action. While it may not be "contraindicated" to administer a second dose of glucagon if the patient fails to respond to the first, it would be very unwise for a family member to delay calling 911 in the hope that the second dose will work. These points need to be reflected in the label. I would suggest: " The dose may be repeated if the patient fails to respond (5 minutes after iv or 15 minutes after im glucagon). But emergency assistence should be sought because intravenous glucose MUST be given if the patient fails to respond to the second dose...."

This statement is consistent with the most current edition of reference 1, USPDI Drug Information for the Health Care Professional which is the 17th edition 1997. Also to be consistent with this reference that mg doses in the table should be changed to USP units.

APPEARS THIS WAY
ON ORIGINAL

SUMMARY AND RECOMMENDATIONS:

This application contains convincing evidence that the new product, rGlucagon is therapeutically equivalent to the existing product, animal-sourced glucagon . Having a supply of glucagon which is not dependent on animal sources is clearly in the public interest. As discussed earlier, the very small difference in blood levels after subcutaneous administration is of no clinical significance. From the study of repeated injections, there is no evidence of tachyphylaxis and no evidence of an immunological response to either rGlucagon or E Coli proteins. Pending Lilly's making satisfactory revisions to the label, I recommend that this NDA be approved.

/S/

Robert I Misbin MD
Medical Officer
February 4, 1998

APPEARS THIS WAY

APPEARS THIS WAY

/S/ 2/6/98

G Alexander Fleming MD
Team Leader

APPEARS THIS WAY

Group Leader's Note

NDA 20-928
glucagon
Lilly

August 29, 1998

The sponsor has adequately shown that this glucagon drug product, produced by recombinant DNA technology, is bioequivalent to its marketed bovine-sourced product.

APPEARS THIS WAY
ON ORIGINAL

Recommendation: The NDA should be approved with the revised labeling (revision #5) recommended by the Division.

/S/

Alexander Fleming, M.D.

cc:
HFD-510
/NDA
/div. file

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20928

CHEMISTRY REVIEW(S)

Phee

JUL 21 1998

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing and Controls

NDA #: 20-928
CHEMISTRY REVIEW #: 2 **DATE REVIEWED:** 07-20-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-11-98	12-12-98	12-15-98
AMENDMENT	6-8-98	6-9-98	6-20-98
AMENDMENT	7-1-98	7-2-98	7-2-98

NAME & ADDRESS OF APPLICANT: Eli Lilly and Co.
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME

Proprietary:	N/A
Nonproprietary/Established/USAN:	Glucagon Injection (rDNA origin)
Code Name/#:	MP-123456B
Chem.Type/Ther.Class:	3 P

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Antihypoglycemic

DOSAGE FORM:	Injection
STRENGTHS:	1 mg
ROUTE OF ADMINISTRATION:	Injection
DISPENSED:	_X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

RELATED DOCUMENTS:

IND

CONSULTS:

REMARKS:

The amendment of 6-8-98 contains the sponsor's responses to the CMC information request letter from Chemistry Review #1 . The sponsor' responses to these items are acceptable. Further, there are Phase IV commitments Lastly, in response to consumer complaints, the sponsor has amended (dated 7-1-98) the labeling for the Glucagon Emergency Kit to include instructions for re-inserting the threaded plunger rod back into the stopper of the Hyporet in the event that it becomes unscrewed during packaging or shipping. These changes are acceptable. There are no further CMC issues with regard to this application.

CONCLUSIONS & RECOMMENDATIONS:

The sponsor has adequately addressed all of the deficiencies noted in Chemistry Review #1. The facilities for manufacture have all been given "ACCEPTABLE" ratings.

This application may be APPROVED based on CMC review.

cc:
Org. NDA 20-928
HFD-510/Division File
HFD-510/WBerlin/Smoore
HFD-510/CSO

APPEARS THIS WAY
ON ORIGINAL

/S/

William K. Berlin, Review Chemist

R/D Int by: SMoore

/S/

7-21-98

filename: MSWfiles\NDA1998\20928\chemrev2.001

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APPEARS THIS WAY
ON ORIGINAL

MAY 20 1998

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing and Controls

NDA #: 20-928
CHEMISTRY REVIEW #: 1 **DATE REVIEWED:** 05-20-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-11-98	12-12-98	12-15-98
AMENDMENT	5-4-98	5-5-98	5-7-98

NAME & ADDRESS OF APPLICANT: Eli Lilly and Co.
Lilly Corporate Center
Indianapolis, IN 46285

APPEARS THIS WAY ON ORIGINAL

DRUG PRODUCT NAME

Proprietary:	N/A
Nonproprietary/Established/USAN:	Glucagon Injection (rDNA origin)
Code Name/#:	MP-123456B
Chem.Type/Ther.Class:	3 P

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Antihypoglycemic

DOSAGE FORM: Injection
STRENGTHS: 1 mg
ROUTE OF ADMINISTRATION: Injection
DISPENSED: _X_ Rx __ OTC

APPEARS THIS WAY ON ORIGINAL

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

The molecular formula is $C_{153}H_{225}N_{43}O_{49}S$, and the molecular weight is 3482.8 Da.

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS:

IND

CONSULTS:

The microbiology portion of the Drug Product section was reviewed by the ONDC Microbiology Staff, HFD-805. The amendment of 2-10-98 contained the sponsor's answers to questions made by the microbiology reviewer. The application was recommended for approval for issues concerning microbiology

There will be no Trade Name for this product, and it will be marketed as "Glucagon for Injection (rDNA origin)".

REMARKS:

CONCLUSIONS & RECOMMENDATIONS:

The sponsor has provided adequate drug substance characterization data, as well as process description information. Process validation was extensive and acceptable. It is reasonable to assume that the recombinant product and the glandular product are equipotent and are of similar quality. The drug product formulation and diluent formulation are unchanged with respect to the approved glandular product, and the primary containers/closures for these are also unchanged.

From a chemistry point of view, this NDA is approvable, pending satisfactory response to deficiencies and comments, and acceptable CGMP inspection. Issue an information request letter.

cc:

Org. NDA 20-928
HFD-510/Division File
HFD-510/WBerlin/Smoore
HFD-510/CSO
HFD-102/JJGibbs

APPEARS THIS WAY
ON ORIGINAL

/S/ 5/20/98

William K. Berlin, Review Chemist

R/D Int by: SMoore /S/ 5/20/98

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APPEARS THIS WAY
ON ORIGINAL

AE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20928

PHARMACOLOGY REVIEW(S)

NDA20-928 April 16, 1998

Eli Lilly and Company
Indianapolis, IN 46285
Jennifer L. Stotka, M.D., Regulatory Director
317-276-2000

APR 21 1998

Submission: Dec, 10, 1997 Received : Dec. 12, 1997

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Summary

Drug: Glucagon for Injection (rDNA)

Related: IND

Table of Contents

RECOMMENDATION: Pharmacology recommends approval of Glucagon for Injection (rDNA) for the proposed indication with labeling revision.

/S/

Herman M. Rhee, Ph.D
Pharmacologist

cc: Original NDA, HFD-510, HFD-345
Ronald Steigerwalt/H. Rhee/J. Rhee

/S/

04/21/98

NDA20-928 April 16, 1998

Eli Lilly and Company
Indianapolis, IN 46285
Jennifer L. Stotka, M.D., Regulatory Director
317-276-2000

Submission: Dec, 10, 1997 Received : Dec. 12, 1997

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Summary

Drug: rDNA Glucagon for Injection, LY021411

Related:

IND
IND
IND

Indication: Treatment for hypoglycemia and diagnostic aid for radiological test

Structural Formula: 29 amino acid, single-chain polypeptide hormone that is identical to natural human glucagon. It is derived from recombinant DNA technology by Eli Lilly and Co. MW3483

Clinical: Human subcutaneous dose of glucagon is 1 mg(0.015 mg/kg for a 70-kg person).

I. PHARMACOLOGY:

A. General:

The glucodynamic and pharmacokinetic effects of recombinant glucagon were investigated in CD rats and beagle dogs following daily i.v. injection for 4 weeks. Rats received doses of 0, 0.2,

1.0, or 5.0 mg , while dogs received doses of 0, 1.0, or 5.0 mg. Blood glucose in treated rats was elevated by approximately 40% after the high dose (5 mg/kg) in male rats. In in female rats the effect was not pronounced after the administration of the same doses(Pharmacol. Toxicol. 73:103, 1993). Blood glucose concentration-time profile in dogs were also monitored. At 5 minutes after i.v. dosing, glucose levels were increased by a factor of 2 to 3. The glucose concentrations returned to baseline levels by about 2 hours. The glucodynamic response to a subcutaneous injection of glucagon was both rapid and short-lived. In most dogs, the serum concentrations of glucose reached a maximum within 10 to 30 minutes after injection and returned to baseline within 1 to 2 hours.

Conscious beagle dogs received subcutaneously doses of 0, 0.02, 0.15 or 1 mg r-Glucagon/kg to test its effects on cardiovascular parameters. Treatment with 0.02 mg produced no effects. Treatment with 0.15 or 1 mg decreased pulse pressure and arterial pressure with comparable increases in heart rate Left ventricular inotropic state was increased and left ventricular EDP was decreased in animals receiving 1 mg. No electrocardiographic abnormalities were noted at any dose level. A dose of 1 mg/kg in dog will be 27 times of clinical exposure, based on mg/m^2. The clinical dose will be 1 mg.

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B. ADME of rGlucagon in Beagle Dogs(Tox Study#D03095)

1. Methods: Lot# PPD03537. Three beagle dogs/sex/group were given rGlucagon at daily doses of 0(vehicle), 0.02, 0.06, or 0.2 mg/kg subcutaneously for 14 days. Serum samples were obtained on Days 0 and 13 at the following times, 0, 10, 20, 30, 45, 60, 90, and 120 minutes.

2. In the majority of dogs, the serum glucose concentration peaked at 10-20 min following an injection of rGlucagon. It appeared that there might be a gender difference between males and females in AUCs in 13 days after rGlucagon treatment. But, AUCs and GME were not really different on Day 0 and 13 (See table below). The standard deviations were too large to draw meaningful conclusion(Data not shown). The large fluctuation in standard deviation is primary responsible for a lack of drug dose-response relationship in glucose AUCs at Day 0 and 13. There might be a possible saturable response as measured by maximal glucose excursion, which was shown in GME values in male dogs at Day 13.

SUMMARY STATISTICS FOR ADME STUDIES IN BEAGLE DOGS(Study#D03095)

Items	Glucose AUC (mg/dl. min)				Glucose Maximum Excursion(mg/dl)			
Sex	Female Dog		Male Dog		Female Dog		Male Dog	
Dose@	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13
0.00	-17	1919	-549	882	-3	26	-9	8
0.02	1038	5720	542*	1663	50*	109*	40*	41*
0.06	593	2926	627*	2972	44*	76*	58*	76*
0.20	5281*	8127*	971*	3107	103*	115*	74*	82*

II. TOXICOLOGY STUDIES

A. Acute Toxicity of rGlucagon in Fischer 344 Rats(Study# R30895)

1. Methods: rGlucagon bulk lot number was 282EMS and specific lot was PPD03537, 1.15 mg/vial. Five Fischer 344 rats/sex were administered a single intravenous or subcutaneous 20-mg/kg dose of rGlucagon.

2. Results: All animals survived the 2-week observation period after treatment. Following subcutaneous administration of 20 mg rGlucagon/kg, no signs of toxicity were observed. However, immediately following intravenous injection of 20 mg rGlucagon/kg decreased activity and ataxia were noted in all animals; clinical signs returned to normal within 1 hour after dosing. There were no gross pathological findings and no statistical analysis was performed.

B. Subchronic Toxicity

APPEARS THIS WAY
ON ORIGINAL

1. 14-Days Toxicity Studies in Rats

Ten Fischer 344 rats/sex/group were administered daily subcutaneous doses of 0, 0.24, 1, or 4 mg rGlucagon/kg for 2 weeks. All rats survived the 2-week treatment period. There were no treatment-related clinical observations, changes in body weight or food consumption, or ocular effects.

Plasma concentrations of rGlucagon increased linearly with dose and reached peak concentrations at approximately 10 to 20 minutes after treatment. Females had higher apparent clearances, generally producing lower maximum plasma concentration(Cmax) and AUC values compared to males. On Day 14, Cmax and AUC values for both sexes and for each dose group were nearly double those reported on Day O. The difference between Days 0 and 14 was interpreted as being due to a change in bioavailability.

Treatment-related hematological changes included slight increases in thrombocyte and neutrophil counts in females given 4 mg/kg. Increases in glucose, albumin, total protein, and slight decreases in cholesterol and blood urea nitrogen. These hematological changes and clinical chemistry effects might not appear to be toxicologically significant due to the magnitude and direction of the changes. There were slight, dose-related increases in absolute and relative liver weights(8% in the 0.25 mg group and 35% in the 4 mg group) which were not accompanied by distinctive histopathologic correlates or clinical chemistry evidence of liver toxicity.

2. 14-Days Toxicological Studies in Beagle Dogs(Study#D03095)

a. Methods: Lot number was PPD03537. Three beagle dogs/sex/group were given daily subcutaneous doses of 0, 0.02, 0.06, or 0.2 mg rGlucagon/kg for 2 weeks.

b. Results:

All dogs survived to treatment termination. Soft stools were observed in all groups administered rGlucagon. There were no treatment-related effects on body weight or food consumption. Mean heart rate was increased(approximately 58% and 36%) on Days 1 and 14, respectively, which came 30 minutes after treatment of 0.2 mg rGlucagon/kg.

Clinical chemistry changes were limited to increased serum glucose, which peaked 10 to 30 minutes after dose administration. Serum glucose returned to baseline 45 minutes after dose administration Day 0, but had not returned to baseline at the time of the last sample (120 min) on Day 13. A general phenomenon of higher and sustained serum glucose levels in females, compared with males, was observed. Mean relative liver weight (relative to brain weight) increased in females at all doses(20% in the 0.02 mg group and 46% in the 0.2 mg group). These changes were accompanied by hepatocellular hypertrophy and by increased presence of clear vacuoles at all dose levels.

There was a trend toward increased heart rates 30 minutes postdosing in dogs receiving 0.06 mg/kg . Mean heart rate increases of approximately 66 and 41 beats/min were observed 30 minutes postdose on Days 1 and 14 respectively in 0.2 mg/kg group. But, doses of 0.02 and 0.06 mg/kg did not result in significant increases in heart rate as shown below. Waveform evaluation indicated that rGlucagon had no effect on cardiac rhythm, conduction, or repolarization. The high dose, 0.2 mg/kg in dog is 5.4 multiple of clinical dose, based on mg/m^2.

EFFECTS OF GLUCAGON ON HEART RATE(Beats/min) IN BEAGLE DOGS@

Glucagon Dose	Day 001 0 minute	Day 001 30 minutes	Day 14 0 minute	Day 14 30 minutes
0.00 mg/kg	122	115	119	112
0.02 mg/kg	123	125	104	118
0.06 mg/kg	116	143	101	129
0.20 mg/kg	133	181*	110	154*

@ Represents mean heart rate. *Indicates $p<0.05$

III. GENOTOXICITY STUDIES:
(Please also see attachment for previously reviewed work on 6/7/1996.)

A. Effect of compound 021411 on the induction of reverse mutations in Salmonella typhimurium and Escherichia coli using the Ames test(Study#921208AMS3671)

1. Methods: Compound #021411 and Lot#703EP2. Four Salmonella typhimurium strains dependent on exogenous histidine(TA1535, TA1537, TA98, and TA100) and one Escherichia

coli strain dependent on exogenous tryptophan(WP2uvrA) were exposed to rGlucagon either in the presence or absence of a rat liver microsome preparation. The tests were performed on histidine- or tryphophan-deficient media; growth of colonies on these media usually indicates a mutagenic event(Please see table below). Glucagon dose levels were

Effects of rGlucagon on Bacterial Mutations with Metabolic Activation Assay

Treatment	TA1535	TA1537	TA98	TA100	WP2uvrA⁻
Control	13	8	36	122	25
0.3125 mg	16	6	43	159	32
0.625 mg	21	8	48	206	19
1.250 mg	20	11	56	227	25
2.500 mg	20	11	82	306	28
5.000 mg	37	14	97	423	28
2-AA	82	63	251	839	203
2-AA*	129	158	549	1591	626

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2-AA stands for 2-aminoanthracene of which concentrations were 0.625 µg/plate for TA1535 and TA 98; 1.25 µg/plate for TA1537 and TA100; and 5 µg/plate for WP2uvrA, respectively. *indicates the double doses of 2-AA were used for each strains.

Tests with rGlucagon resulted in dose-related increases in colony counts for strains TA98 and TA100 in the activated assay. Increased colony counts were not observed in the nonactivated assays. Representative samples of treated TA98 and TA100 colonies grew when transferred to histidine-free media, indicating that the organisms were true revertants. The reversion was related to generation of histidine from rGlucagon and was not due to a mutagenic impurity. Thus, additional Ames assays were conducted using rGlucagon that had been subjected to further purification. The result indicated that no mutagenic impurities were present in the test article. Rather, the observed increases in colony counts can be explained based on the liberation of histidine, which is essential for the growth of TA98 and TA100, from rGlucagon.

The high concentrations of rGlucagon in the test apparently provided sufficient histidine to allow continued cell divisions and subsequent formation of spontaneous revertants. Thus, it appeared that the Ames bacterial mutation assay method did not serve the assay purpose in this case.

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IV. No reproductive and carcinogenicity studies were performed.

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V. SUMMARY:

The physiology and pharmacology of glucagon has been extensively documented, of which primary effect is elevation of blood glucose through stimulation of glycogenolysis and

gluconeogenesis. Glucagon also has catabolic effects on triglycerides and protein metabolism, increased heart rate, positive inotropism, diuresis, anti-inflammatory effects and inhibition of gastrointestinal spasm. The toxicology and pharmacodynamics of human recombinant glucagon following daily intravenous administration were studied in rats and dogs in this NDA.

Fourteen-day toxicity was studied in Fischer 344 rats. Ten rats/sex were administered up to 4 mg of glucagon per kg body weight subcutaneously for 2-weeks. No deaths were observed and there were no clear signs of treatment-related toxicity. In 2-week studies with three beagle dogs/sex, glucagon(up to 0.2 mg/kg) did not produced mortality, although increased heart rate was observed following intravenous administration of 0.2 mg/kg/day. There were no treatment-related differences in body weight gain and in food consumption. No treatment-related ocular and hematological changes were noted . The mean, absolute, and relative liver and kidney weights of all the treated groups were higher than those of the controls. There was no gross or histopathological evidence of toxicity of any of the organs and tissues examined.

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VI. LABELING: (To be communicated to the sponsor)

Please revise the label statement regarding genetic toxicology as follows:
In a series of studies examining effects on the bacterial mutagenesis (Ames) assay, it was determined that positive findings were related to technical difficulties in running this assay with peptides and were not due to mutagenic activities of the glucagon.

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Please revise the Pregnancy Category statement as follows:
Pregnancy category B- Reproduction studies have not been performed with recombinant glucagon. However, studies with pancreatic glucagon were performed in rats at doses up to 2 mg/kg glucagon administered two times a day (up to 40 times the human dose based on body surface area, mg/m^2), and have revealed no evidence of impaired fertility or harm to the fetus due to glucagon.

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VII. RECOMMENDATION: Letter to the sponsor

Drug exposure comparisons between preclinical and clinical doses should be based on plasma concentration, rather than on mg/kg. If plasma concentrations of the drug are not known, exposure comparison should be based on surface area(mg/m^2).

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VIII. ATTACHMENT:

1. Review of Amendment(Serial#019) dated 6/28/1996

IX. RECOMMENDATION:

Pharmacology recommends approval of rGlucagon for the proposed indication with labeling revision.

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/S/

Herman M. Rhee, Ph.D
Pharmacologist

cc: Original NDA, HFD-510, HFD-345
Ronald Steigerwalt/H. Rhee/J. Rhee

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IND **June 28, 1996**

Sponsor: Lilly Research Laboratories; Indianapolis, IN 46285

Date Submitted: 6/6/96 **Date Received:** 6/7/96

PHARMACOLOGY AND TOXICOLOGY REVIEW
Amendment #019 (June 7, 1996)

DRUG: Glucagon for Injection (recombinant), LY021411.

MEMOS: Positive Ames results were discussed with sponsor on April 6, 1996 (Dr. Jordan from FDA and Dr. Kim Birch from Lilly). Ames test results were requested as well as results with animal source glucagon. This submission provides those data and requests a response. The sponsor wishes to switch from animal source to recombinant glucagon.

REVIEW OF TOXICOLOGY REPORT No. 5:
THE EFFECT OF rGLUCAGON ON THE INDUCTION OF REVERSE MUTATIONS IN *S. typhimurium* AND *E. coli* USING THE AMES TEST

NOTE: Study performed by sponsor. Studies performed Nov. 1995. Study completed:5/30/96. GLP statement was provided. Exception to GLP was that stability under conditions of administration and the concentration of the test and control articles were not determined.

PURPOSE: *In Vitro* assessment of mutagenic potential of recombinant and animal source glucagon using a bacterial mutagenesis assay ("Ames Test").

EXPERIMENTAL DESIGN: Standard plate incorporation assay with 10% S9 (v/v) performed in triplicate. Assay was repeated 6 times with several different batches of rGlucagon. A single test was performed with animal source glucagon. Colonies were counted after 48 h at 37°C. Controls and low dose plates were counted by automated counters. High dose plates (2500 and 5000 :g/plate) were counted manually due to the presence of large and small colonies. Doses tested were: 312.5, 625, 1250, 2500 and 5000 :g/plate. Replica plating was performed to test for determination of frequency of spontaneous vs induced revertants. rGlucagon was subjected to HPLC, dialysis or precipitation in an attempt to remove contaminants, then retested in the Ames assay as above. Release of histidine in Ames matrix was assessed in a separate experiment.
Salmonella Strains: TA98, TA100, TA1535, TA1537.
E.coli: Wp2*uvr*A.
Metabolic Activation System: S9 from commercial source:
Prepared with Aroclor 1254-induced rat livers.

Criteria for positive result: 2-fold increase over controls for TA100, TA98 and WP2*uvr*A for two consecutive concentrations. 3-fold for strains TA1535 and TA1537 for two consecutive concentrations.

RESULTS

Glucagon up to 5000 :g/plate was clearly negative in all assays in all strains in the absence of metabolic activation. A summary table of results in the presence of metabolic activation follows (values represent means of triplicate plates in each assay):

EXPERIMENT#°		951107AMS3671	951128AMS3671A	951128AMS3671B	960116AMS3671	960124AMS3671	960212AMS3671	921208AMS3671 (ANIMAL)
STRAIN	DOSE: g/plate							
TA1535	control	15	10	8	13	13	16	11
	312.5	16	15	13	16	14	13	17
	625	19	12	12	21	16	17	17
	1250	20	22	23	20	20	19	14
	2500	25	28	20	20	17	22	16
	5000	40	32	9	37	42	28	17
TA1537	control	10	9	7	8	10	7	13
	312.5	9	7	8	6	12	15	9
	625	11	7	11	8	11	14	14
	1250	11	9	14	11	13	16	16
	2500	10	7	13	11	23	17	13
	5000	13	8	9	14	18	16	12
TA98	control	30	28	31	36	28	25	28
	312.5	28	35	39	43	35	47	36
	625	31	30	38	48	36	37	39
	1250	66	48	39	56	55	45	40
	2500	71	63	41	82	98	50	40
	5000	68	56	40	97	126	64	29
TA100	control	132	152	185	122	119	115	154
	312.5	185	166	228	159	163	145	175
	625	224	181	220	206	171	146	216
	1250	226	227	204	227	230	232	257
	2500	356	309	317	306	283	237	267
	5000	380	289	249	423	308	253	296
WP2*uvr*A	control	26	29	26	25	28	37	38
	312.5	27	27	24	32	29	54	41
	625	26	28	26	19	40	44	56
	1250	27	20	23	25	35	37	50
	2500	22	21	17	28	30	30	40

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	5000	24	12	32	28	25	33	44

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EVALUATION

Bacterial mutagenesis assays were performed and evaluated according to acceptable criteria for these studies. These studies were performed within the parameters outlined by both ICH and OECD guidelines. The following points can be made:

- The bacterial mutagenesis assay was clearly negative in all bacterial strains for several lots of rGlucagon in the absence of metabolic activation.

- In the presence of metabolic activation, the strains TA1537 and WP2uvrA were clearly negative in six assays using several lots of rGlucagon and a single experiment with animal source glucagon.

- When the criterion for a three-fold increase in colony counts over controls is applied to TA1535, the results are considered negative for rGlucagon in this strain in the presence of metabolic activation. This is a reasonable criterion for determining a positive response since the background colony formation in this strain is very low. However, in consideration of data to be presented later, it is notable that in 5 out of 6 experiments, if the 2-fold increase criterion was followed, the response would have been considered positive for this strain.

- rGlucagon in the presence of metabolic activation was clearly positive in strains TA98 and TA100 in 5 out of 6 experiments. In one experiment, there was a trend to increased colonies in both strains which did not reach significance by the criteria for a positive result. The positive controls in this experiment were within normal ranges, so it does not appear that the lower response in this assay was due to an overall low performance of this particular assay.

- In light of the above, it is necessary to point out that the positive responses were limited to the 2500 and 5000 :g/plate doses. In each assay with rGlucagon, the plates at these doses had to be counted manually due to the presence of large and small colonies making automated counting difficult. This appears to be problematic for two reasons: 1) the presence of large and small colonies on these plates may indicate that artifact may have been induced at these doses and 2) by manually counting colonies, it is possible that a counting artifact could have been introduced, contributing an apparent increase in colony number at these high doses in addition to the "feeding effect" proposed by the sponsor.

- In the single assay provided for animal source glucagon, the response was clearly negative for TA1535, TA1537, TA98 and WP2uvrA in the presence of metabolic activation. Positive controls were what might be expected for this assay and tended to be actually on the high side compared to the experiments for rGlucagon. There was a trend which was close to the criteria for a positive response in TA100. Interestingly, the high dose colony counts were similar to other assays which were positive for rGlucagon, but the controls were higher which contributed to the negative classification for this experiment.

- The sponsor also performed a replica plating assay where colonies were

replated to) plates. Colonies from treated plates were taken from the high dose only. It appeared that colonies grew successfully on both plate types, **indicating that the colonies were revertants.**

- rGlucagon was subjected in an attempt to remove any low molecular weight soluble contaminants. The resulting components were tested in TA98 and TA100. The results remained positive at similar levels to "unpurified" rGlucagon, indicating that the positive response is not likely to be due to a small soluble contaminant.

- In a separate experiment, it was determined that histidine is released from rGlucagon after incubation with Ames matrix which includes S9 mix. Maximum levels released under the conditions of the assay was 0.51 mM. It is not known how much would be liberated under the conditions of the actual Ames assay.

CONCLUSIONS

1.) experiments indicated that the positive Ames results are not due to a low molecular weight **soluble** contaminant.

2. Histidine may be released into the medium by the Ames but it seems unlikely that the "feeding effect" proposed by the sponsor is the cause for the positive response since the replica plating experiment indicated that the colonies at the high dose were, in fact, revertants. One would expect that at least a significant portion of these colonies would not be revertants if there was a "feeding effect". In regards to the "feeding effect", why would the strains respond differently if there was such an effect?

3. Given the different character of the colonies in the high dose plates (small and large) and the fact that the positive responses were found in the hand counted plates while the remaining plates were counted automatically, it seems possible that there may be some methodological problems at the doses that appeared to be positive.

4. Unlike rGlucagon, animal source glucagon was negative in TA98. However, there did appear to be a positive trend in TA100 which, while not strictly positive in this assay, was of similar magnitude to the response in three of the six assays with rGlucagon. Further experiments with the animal source glucagon could support this. It is this negative response in the animal source product that suggests that there may still be a difference in the two products.

TO BE COMMUNICATED TO SPONSOR

We have evaluated the data on the bacterial mutagenesis experiments which compare recombinant and animal source glucagon and have come to the following conclusions:

1. , experiments indicated that the positive Ames results are not due to a low molecular weight soluble contaminant.
2. Histidine may be released into the medium by the Ames , but it seems unlikely that the "feeding effect" is the cause for the positive response since the replica plating experiment indicated that the colonies at the high dose were, in fact, revertants. One

would expect that at least a significant portion of these colonies would not be revertants if there was a "feeding effect". It is also not clear why there would be a different response in the various strains if such an effect was responsible.

3. Given the different character of the colonies in the high dose plates (the finding of small and large colonies which are apparently not present at lower doses) and the fact that the positive responses were found in the hand counted plates while the remaining plates were counted automatically, it seems possible that there may be some methodological problems at the doses that appeared to be positive.

4. Unlike rGlucagon, animal source glucagon was negative in TA98. However, there did appear to be a positive trend in TA100 which, while not strictly positive in this assay, was of similar magnitude to the response in three of the six assays with rGlucagon. It is this negative response in the animal source product that suggests that there may still be a difference in the two products.

5. Further experiments with animal source glucagon could confirm the conclusion that the positive response with rGlucagon was due to a property of glucagon rather than a contaminant, particularly if repeat experiments with the animal source material were positive. However, given the potential methodological problems outlined in point 3 above and that a similar, though not strictly positive, response was noted with animal source glucagon, we do not feel that it is necessary to pursue this.

6. In summary, we agree that the positive results in the Ames test is due to either a property of the glucagon protein or a methodological problem in conducting these experiments at the high dose levels. We also believe that the "feeding effect" is an unlikely explanation for these positive responses.

/S/

Ronald W. Steigerwalt, Ph.D.

cc: IND
HFD510
HFD510/Misbin/Steigerwalt/J.Rhee

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20928

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

FEB 23 1998

Microbiologist's Review #1 of NDA 20-928
February 12, 1998

A. 1. **APPLICATION NUMBER:** 20-928

APPLICANT: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

2. **PRODUCT NAMES:** Glucagon for injection (rDNA origin)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Sterile lyophilized powder containing glucagon, 1mg (1U) dosage in a 1 ml vial, accompanied by Hyporets Diluting solution (1 ml) for reconstitution in a 1 ml syringe. Glucagon for injection is to be administered by subcutaneous, intramuscular and intravenous injection. It is for single use, a non-preserved product.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Glucagon is indicated as a treatment for severe hypoglycemia in patients with type 1 diabetes. It is also used as a diagnostic aid in the radiological examination of the stomach, duodenum, small bowel, and colon when diminished intestinal motility would be advantageous.

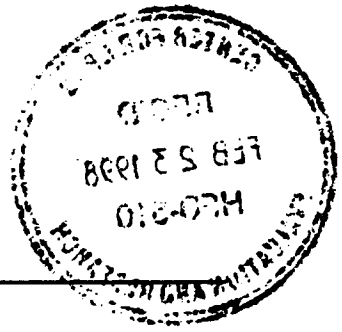
B. 1. **DATE OF INITIAL SUBMISSION:** December 11, 1997

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:** Facsimile from Lilly: Response to Microbiologist's request of information (2/10/98).

4. **ASSIGNED FOR REVIEW:** December 22, 1997

5. **DATE OF CONSULT REQUEST:** December 18, 1997



C. REMARKS:

rGlucagon for Injection is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. It is a single chain of 29 amino acid residues. Glucagon is produced

The

Hyporets

D. CONCLUSIONS:

The validation data of the drug product are adequate for sterility assurance. The submission is recommended for approval for issues concerning microbiology.

/S/ 2/12/98

Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 2/23/98

cc:

NDA 20-928
HFD-510/ Div. File
HFD-805/ Uratani
HFD-510/CSO/J. Rhee
drafted by: Brenda Uratani, 2/12/98
R/D initialed by P. Cooney, 2/12/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20928

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

HFD-510 Rhee

MAY 26 1998

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-928/N-000	**SUBMISSION DATE:**	**11-DEC-97** **16-JAN-98** **04-MAY-98**
BRAND NAME:	**Glucagon for Injection (rDNA origin)**	
GENERIC NAME:	**Glucagon for Injection (rDNA origin)**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Eli Lilly and Co., Indianapolis, IN**	
TYPE OF SUBMISSION:	**N-000: Original NDA, Code 3P**	

TERMS AND ABBREVIATIONS:

AUCa-b ..... Area under the plasma-concentration-time curve from time a to time b
BGmax ..... Maximum observed plasma glucose concentration
TBGmax..... Time to maximum observed plasma glucose concentration
Cmax... ..... Maximum plasma concentration
DMEDP ..... Division of Metabolic and Endocrine Drug Products
IM..... ..... Intramuscular
IV..... ..... Intravenous
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics
SC..... ..... Subcutaneous
Tmax... ..... Time to maximum plasma concentration

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SYNOPSIS:

Currently, glucagon is available only from animal sources. Eli Lilly developed a recombinant glucagon product (rDNA glucagon; rglucagon). Study H3F-LC-GFAA, submitted in this NDA, demonstrated that the rGlucagon product is bioequivalent to the approved animal source glucagon when administered SC or IM.

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RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 20-928/N-000 submitted 11-DEC-97 and 16-JAN-98. The overall Human Pharmacokinetic Section is acceptable to OCPB and supports approval of this submission. This recommendation and labeling comments (p. 8) should be sent to the sponsor as appropriate.

Table of Contents **Page**

(Appendices and/or Attachments available from DPE-II upon request)

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BACKGROUND:

Glucagon is a single-chain polypeptide hormone consisting of 29 amino acid residues (Figure 1). It has a molecular weight of 3483 Daltons and its structure is conserved in many mammalian species (e.g., human, bovine, porcine, rat, canine). Eli Lilly markets glucagon produced from either bovine or porcine (animal) sources. Glucagon is indicated for the treatment of hypoglycemia and as a diagnostic aid to relax the intestinal tract during radiographic examination.

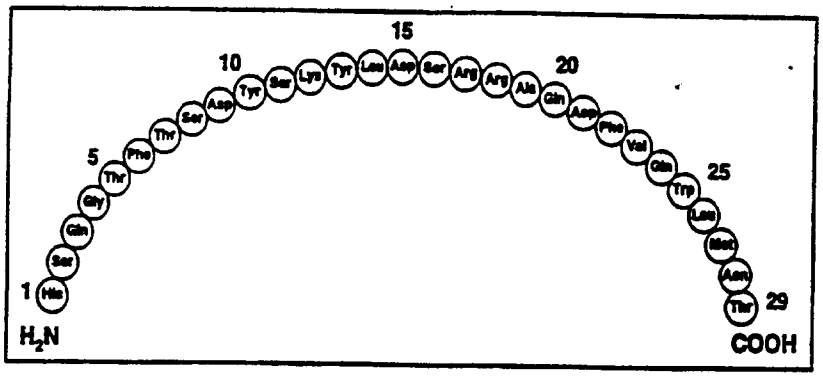

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Figure 1. Glucagon structure

Eli Lilly claimed to have developed a recombinant DNA glucagon (rGlucagon). The diluent currently supplied with the animal-source glucagon

submitted a study to establish the bioavailability and bioequivalence of the animal and recombinant products.

rGlucagon has not yet been marketed anywhere in the world.

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VOLUMES REVIEWED: 1.1, 1.3, 1.21-1.23.

PROTOCOL INDEX

Protocol Number	Title	Page
H3F-LC-GFAA	Comparison of Pharmacokinetic Parameters of Recombinant and Animal-Source Glucagon After IV, IM, and SC Injection	p. 20

DRUG FORMULATION:

As per submission on 16-JAN-98, the rGlucagon used in Study H3F-LC-GFAA was of the commercial batch size and was manufactured using the commercial process.

ANALYTICAL METHODOLOGY:

Assay of plasma samples for Glucagon was conducted using a

). These assays are acceptable to OCPB.

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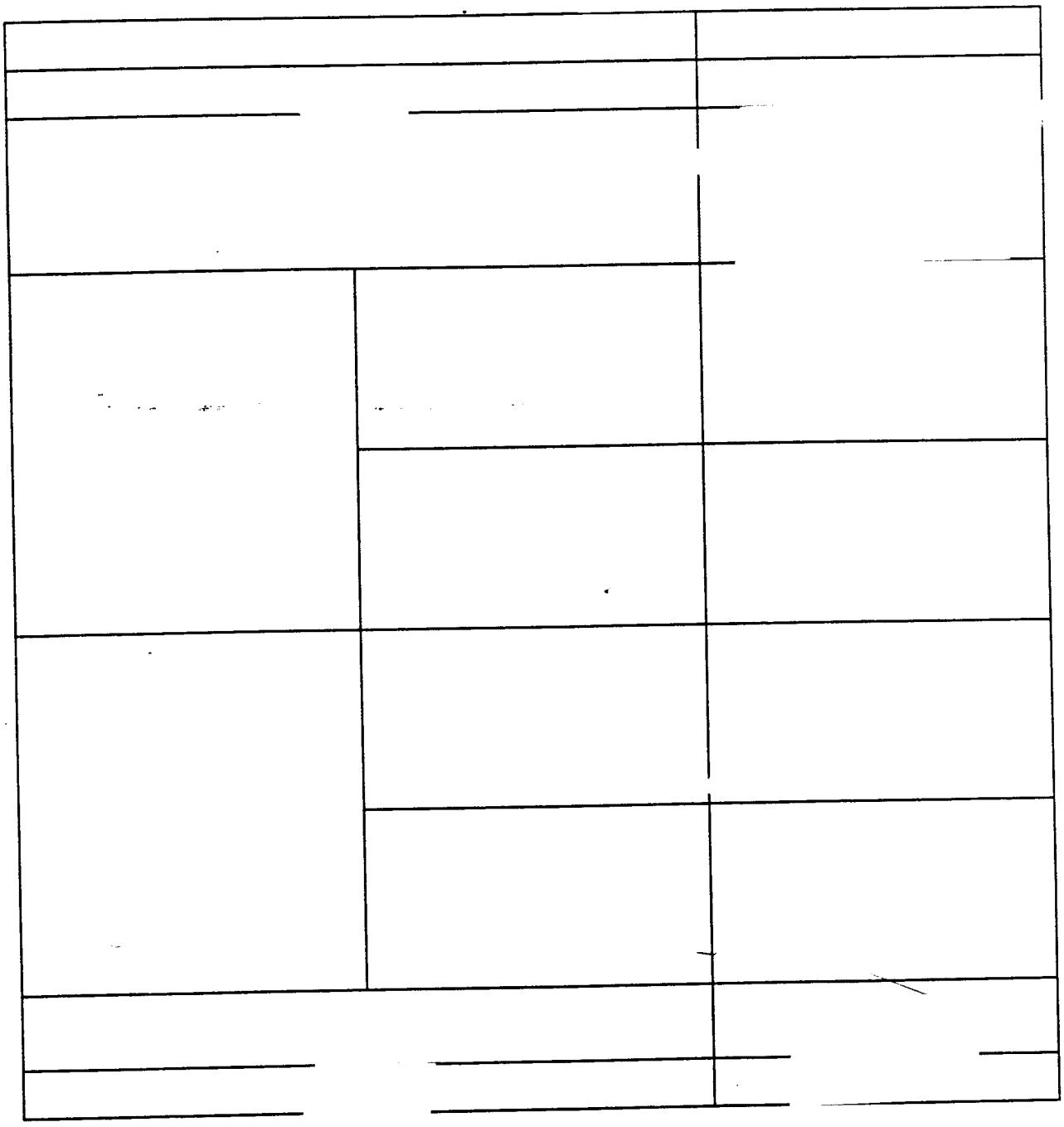

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HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

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ON ORIGINAL

A. Absolute Bioavailability

Table GFAA.4.21. Mean (±SD) Pharmacokinetic Parameters, Intravenous Administrations

	$t_{½}$, hours	C_{max}, ng/ml	t_{max}, hours	$AUC_{(0-t)}$, ng•hr/ml	$AUC_{(0-inf)}$, ng•hr/ml	CL L/h	V_{ext} L
rGlucagon 0.25 mg (A)	0.128±0.0570	37.4±9.24	0.044±0.017	4.07±0.631	4.08±0.632	62.5±9.00	11.9±6.55
rGlucagon 0.5 mg (B)	0.153±0.0930	77.6±20.7	0.051±0.027	8.47±1.83	8.48±1.84	61.1±11.3	12.7±6.88
rGlucagon 1.0 mg (C)	0.222±0.120	171±67.3	0.047±0.019	17.9±4.04	17.9±4.04	58.4±13.3	18.5±10.7
rGlucagon 2.0 mg (D)	0.299±0.0944	368±117	0.045±0.016	37.7±6.98	37.7±6.97	54.6±10.1	23.8±9.20
p-value	0.0005I*	0.186H	0.757I	0.0991H	0.104H	nc	nc

* statistically significant difference ($\alpha = 0.05$)
H - from regression of dose-normalized parameter values versus dose, test of hypothesis slope = 0
I - from the ANOVA comparing treatment means
nc - not compared

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Table GFAA.4.21 indicates the pharmacokinetic parameters for rGlucagon when administered as an IV bolus injection (N=10). Generally, there is consistency of pharmacokinetic parameters between the doses. T½ may be extended, and CL diminished, for the higher doses because the glucagon concentrations are detectable for a longer period of time with higher doses. As the table indicates, there are no significant differences between Cmax, Tmax, or AUC for the different doses. Figures 2 and 3 indicate the dose-normalized Cmax and AUC for the four doses.

It is generally accepted that the 1 mg dose of glucagon is within the top of the dose-response curve (i.e., greater than the minimum dose needed to see the maximum response). This is supported by the blood glucose data which indicated that, for all four doses, the BGmax was and was not significantly different between the four treatment groups.

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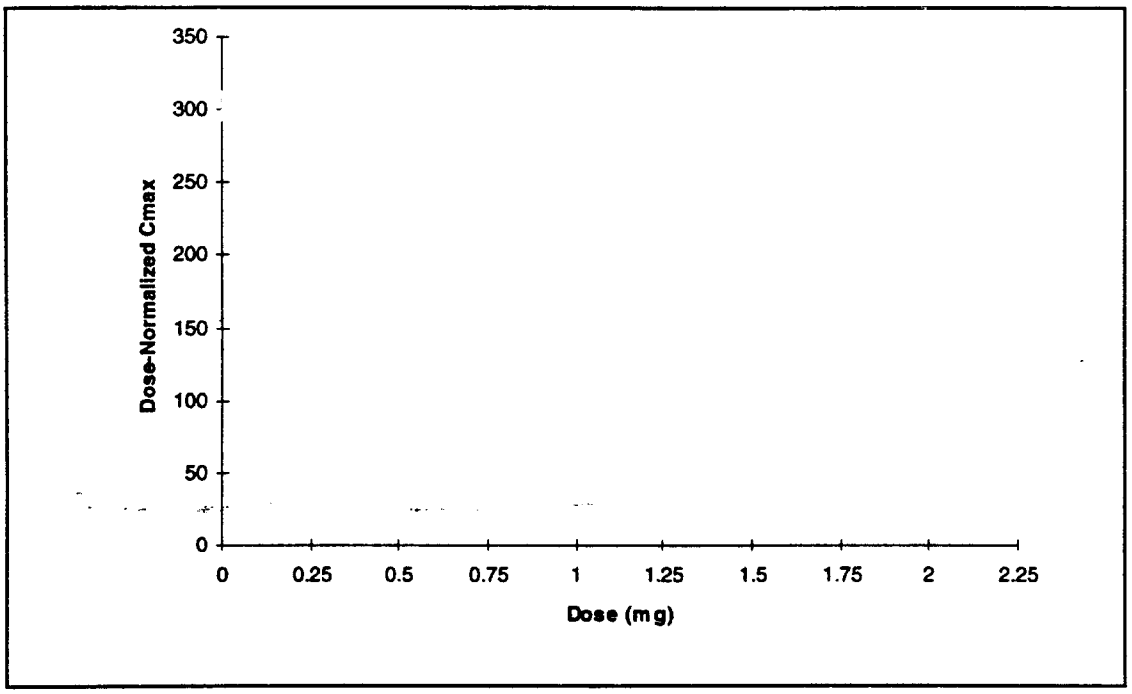

Figure 2. Dose-normalized Cmax after IV bolus of rGlucagon, r=0.89, N=10.

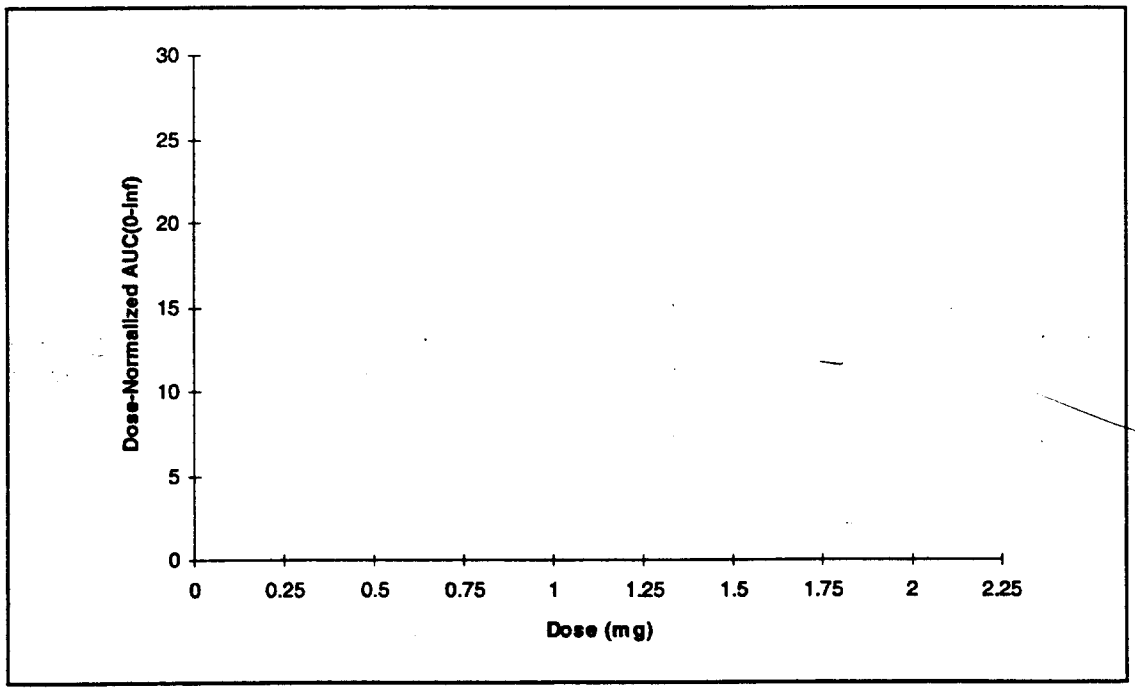

Figure 3. Dose-normalized AUC after IV bolus of rGlucagon, r=0.96, N=10.

B. Bioequivalence

For glucagon, Cmax, Tmax, T½, AUC0-t, and AUC0-inf were calculated (Tables 3 and 4). For blood glucose, BGmax is the relevant pharmacodynamic parameter; these parameters were generated with baseline-corrected blood glucose concentrations. 90% confidence intervals were constructed on the difference between the pharmacokinetic and pharmacodynamic Ln-transformed data for each route of administration (i.e., SC parameters were not compared with IM parameters).

Table 3. Mean ± SD Pharmacokinetic Parameters and 90%CI for glucagon SC.

	$t_{½}$, hours	C_{max}, ng/ml	t_{max}, hours	$AUC_{(0-t)}$, ng•hr/ml	$AUC_{(0-inf)}$, ng•hr/ml
Animal-source pH=2.8 (A)	0.488 ± 0.166	9.12 ± 5.11	0.33 ± 0.10	6.57 ± 2.29	6.63 ± 2.30
Recombinant pH=2.8 (B)	0.451 ± 0.146	10.0 ± 3.65	0.27 ± 0.11	6.43 ± 2.15	6.47 ± 2.15
Recombinant pH=2.0 (C)	0.461 ± 0.166	7.94 ± 3.83	0.35 ± 0.098	5.82 ± 1.61	5.87 ± 1.62
		90 % CI		**90 % CI**	**90 % CI**
B vs. A[a]		102-126		91.4-109	91.2-109
C vs. A[a]		79.1-97.8		82.4-98.2	82.4-98.1
C vs. B[a]		69.8-86.3		82.5-98.4	82.8-98.5

a. N=25.

The mean Cmax and AUC0-inf ratios for SC rGlucagon to animal-source glucagon (C vs. A; the comparison of interest) are 0.88 and 0.90. The Cmax of the rGlucagon tends to be slightly lower than the animal-source glucagon. However, given that: 1) a 0.25 mg IV dose of glucagon elicited the same pharmacodynamic response as a 2 mg IV dose (See IA above), and 2) the pharmacodynamic response was not significantly different between any formulation given SC or IM (See below), this trend toward a lower Cmax is not of clinical concern.

Table 4. Mean ± SD Pharmacokinetic Parameters and 90%CI for glucagon IM.

	$t_{½}$, hours	C_{max}, ng/ml	t_{max}, hours	$AUC_{(0-t)}$, ng•hr/ml	$AUC_{(0-inf)}$, ng•hr/ml
Animal-source pH=2.8 (D)	0.414 ± 0.147	7.36 ± 2.51	0.22 ± 0.10	4.31 ± 1.36	4.36 ± 1.38
Recombinant pH=2.8 (E)	0.382 ± 0.100	7.81 ± 3.57	0.21 ± 0.11	4.62 ± 1.86	4.67 ± 1.87
Recombinant pH=2.0 (F)	0.364 ± 0.141	6.90 ± 2.64	0.22 ± 0.095	3.92 ± 1.48	3.97 ± 1.49
		90 % CI		**90 % CI**	**90 % CI**
D vs. E[a]		93.6-115		97.1-115	97.4-116
D vs. F[a]		85.2-105		83.6-99.5	83.8-99.6
E vs. F[a]		82.1-101		78.9-93.9	79.1-93.9

a. N=25.

The mean Cmax and AUC0-inf ratios for IM rGlucagon to animal-source glucagon (D vs. F) are 0.95 and 0.91. The 90% CI are within the 80-125 interval.

Table 5. Mean (SD) Pharmacodynamic Parameters and 90%CI for glucose (SC glucagon inj.)

	BG_{max}, mg/dL	TBG_{max}, hours
Animal-source pH=2.8 (A)	133 (20.6)	0.49 (0.46)
Recombinant pH=2.8 (B)	132 (19.0)	0.43 (0.18)
Recombinant pH=2.0 (C)	136 (19.8)	0.52 (0.54)
	90% CI	
B vs. A[a]	96.2-103	
C vs. A[a]	99.2-106	
C vs. B[a]	99.8-107	

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Table 6. Mean (SD) Pharmacodynamic Parameters and 90%CI for glucose (IM glucagon inj.)

	BG_{max}, mg/dL	TBG_{max}, hours
Animal-source pH=2.8 (D)	137 (22.3)	0.37 (0.14)
Recombinant pH=2.8 (E)	143 (20.6)	0.43 (0.15)
Recombinant pH=2.0 (F)	138 (16.5)	0.45 (0.16)
	90% CI	
E vs. D[a]	101-108	
F vs. D[a]	96.7-103	
F vs. E[a]	92.6-98.7	

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There were no significant differences in BGmax or TBGmax for any of the 6 treatments. The 90%CI for the blood glucose response after either SC or IM administration indicated that there is therapeutic equivalence between the rGlucagon and animal-source glucagon products.

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CONCLUSIONS:

Study H3F-LC-GFAA, submitted in this NDA, demonstrated that the rGlucagon product is bioequivalent and therapeutically equivalent to the approved animal-source glucagon when administered SC or IM.

APPEARS THIS WAY ON ORIGINAL

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

Robert M. Shore, Pharm.D. /S/ 21-MAY-98
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

APPEARS THIS WAY
ON ORIGINAL

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 21-MAY-98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 5/26/98

CC: NDA 20-928/N-000 (orig.,1 copy), HFD-510(RheeJ, Misbin), HFD-340 (Viswanathan), HFD-850(Lesko, Huang), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: AE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix 1. Labeling as Submitted 04-MAY-98

APPEARS THIS WAY
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8 Page(s) Redacted

DRAFT LABELING

Appendix 2. Study summaries

Name of company:	Summary table referring to Part of the dossier.	(For National Authority use only)
Name of finished product:	Volume: Page:	
Name of active ingredient:		

Clinical Study Synopsis: Study H3F-LC-GFAA

Title: Comparison of Pharmacokinetic Parameters of Recombinant and Animal-Source Glucagon After IV, IM, and SC injection

Investigator:

Study Centers: Single-center study.

Dates of Study: October 1996 through November 1996

Clinical Phase: Phase 1

Objectives: This protocol had several objectives:
to establish bioequivalence of recombinant glucagon (rGlucagon) at 2 separate pH values (2.8, 2.0) with existing animal-source glucagon (pH 2.8) after subcutaneous (SC) and intramuscular (IM) administrations to compare the safety profiles of rGlucagon and animal-source glucagon to determine the dose response, glucodynamic and pharmacokinetic behavior of rGlucagon after intravenous administration.

Methodology: This study was divided into two parts: Part I, a randomized intravenous dose-ranging study of rGlucagon (pH 2.8), and Part II, an open-label, randomized, 6-way crossover design for the assessment of bioequivalence between animal-source glucagon and rGlucagon with two separate pH values of rGlucagon. Parts I and II were performed in a parallel fashion, with separately enrolled panels. Neither Part I nor Part II were blinded.

Number of Subjects: Part I: Male 8, Female 4, Total 12;
Part II: Male 15, Female 14, Total 29.

Diagnosis and Inclusion Criteria: Healthy subjects.

Dosage and Administration: Part I: rGlucagon: 0.25, 0.5, 1.0, and 2.0 mg single IV dose
Part II: Test Product
rGlucagon: 1 mg given as a single SC and IM dose
Reference Therapy
Animal-source glucagon: 1 mg given as a single SC and IM dose

Duration of Treatment: Part I: rGlucagon: 1 day/dose x 4 doses separated by 7-10 days
Part II: rGlucagon: 1 day/dose x 6 doses separated by 7-10 days
Animal-source glucagon: 1 day/dose x 6 doses separated by 7-10 days

Criteria for Evaluation:

Pharmacokinetics-- Glucagon concentrations/pharmacokinetic parameters.
Efficacy-- Glucose measurements/glucodynamic parameters.
Safety-- Safety parameters included vital signs, clinical laboratory tests, heart rate, blood pressure, temperature, and respiratory rate were monitored throughout the study.

Methods:

Bioanalytical:

Pharmacokinetic--Plasma glucagon concentrations were analyzed

Efficacy Measures--Serum glucose concentrations were analyzed

Statistical--Part I: ANOVA procedures were used to compare dose-normalized pharmacokinetic parameters. Dose linearity was further assessed by linear regression techniques. Similar ANOVA analysis of the pharmacodynamic parameters was conducted with pairwise differences between treatments assessed using Bonferroni t-tests. Part II: Pharmacokinetic and pharmacodynamic parameters were analyzed in accordance with a six-way crossover design. 90% confidence intervals were established for the determination of bioequivalence.

Summary and Conclusions:

Part I (IV Dose-Ranging): rGlucagon pH 2.8 exhibited dose proportionality in plasma glucagon C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ when administered intravenously in doses ranging from 0.25 to 2.0 mg. There was no statistically significant difference in glucose response between the glucagon doses. Maximum blood glucose concentration, time to maximum blood glucose concentration, maximum absolute excursion, time of maximum absolute excursion, glucose excursion AUC, and $AUC_{(0-rtb)}$ were similar among the treatments.

Part II (SC Bioequivalence Determinations): Pharmacokinetic comparisons of the SC administrations showed all treatments met standard bioequivalence criteria with respect to AUC.. The comparison of rGlucagon pH=2.0 to both references also met standard bioequivalence criteria for AUC. The treatments differed only in C_{max}. On average, rGlucagon pH 2.8 had the highest C_{max}, and rGlucagon pH 2.0 the lowest. Comparisons of the SC treatments showed glucodynamic equivalence for maximum blood glucose concentrations and maximal absolute excursion values met standard bioequivalence criteria rGlucagon pH 2.8 and animal-source glucagon showed glucodynamic equivalence for $AUC_{(0-rtb)}$. Broad confidence intervals contributed to the inbioequivalence. rGlucagon pH 2.0 produced the highest overall blood glucose response following SC administration.

Part II (IM Bioequivalence Determinations): Pharmacokinetic comparisons following IM administration met standard bioequivalence criteria between animal-source glucagon and both recombinant formulations with respect to C_{max} and $AUC_{(0-t)}$. As with the SC treatments, glucodynamic comparisons showed all the treatments had equivalent maximum blood glucose concentrations and maximum absolute glucose excursion. Animal-source glucagon showed glucodynamic equivalence to both recombinant formulations with respect to blood glucose versus time area under the curve values.

rGlucagon and animal-source glucagon appeared to be equally safe and well tolerated by the study participants during this trial. The most common adverse events reported were nausea, dizziness, and headache, occurring throughout both treatment groups.

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REVIEWER'S COMMENTS FOR STUDY GFAA:

1. For parts 1 and 2, 10 and 25 subjects, respectively, were included in the final analysis. All subjects were between 23 and 60 years old. Only one out of 6 drop-outs was due to AE; this was from the currently marketed formulation.

2. Agree with results.

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20928

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

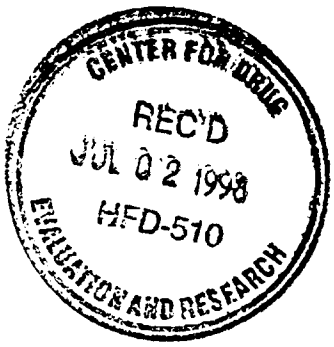
B2

AMENDMENT
ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



July 1, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Patient Insert Draft Labeling
Revision #2

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to phone conversations between Dr. Bill Berlin (FDA) and Ms. Ann Maloney, Eli Lilly and Company (Lilly) on June 24, 1998 and between Dr. Bill Berlin and Dr. Kim Birch (Lilly) on June 25, 1998 regarding a customer complaint concerning the animal glucagon diluent hyporet. We are herewith providing new draft labeling for the recombinant glucagon labeling, Information for the Patient insert (revision #2), that addresses the potential that the plunger rod can become disconnected from the rubber stopper prior to or during use. In addition minor changes to the cartons for the Glucagon Diagnostic Kit and Glucagon Emergency Kit are also provided.

All labeling changes are depicted in **large bold font** and are summarized below. Draft labeling is provided in both paper and electronic format. The diskette has been determined to be free of viruses.

Information for the User, Directions for Use To Prepare Glucagon For Injection, step number 4

1. The word "gently" has been added to the phrase, "Using the same syringe, hold bottle upside down and, making sure the needle tip remains in solution, gently withdraw all of the solution (1 mg mark on syringe) from bottle." to minimize the likelihood of the plunger rod detaching from the rubber stopper.
2. The word "plunger" has been replaced with "rubber stopper" to accurately reflect the function of the plastic clip.
3. The phrase, "however, if the plastic plunger rod separates from the rubber stopper, simply reinsert the rod by turning it clockwise." has been added to provide the user with proper instructions in the event that the plastic plunger rod detaches from the rubber stopper.

Carton Labels for Glucagon Diagnostic Kit and Glucagon Emergency Kit

1. The word "gently" has been added to the sentence, "Mix well and gently withdraw the entire contents of the vial back into the syringe." for labeling consistency.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

for Gregory Enas, Ph.D.
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
/S/ 7-25-98
CSO INITIALS DATE

Enclosures

CC: Dr. Robert Misbin (FDA) Desk Copy (paper copy only)
Dr. Bill Berlin (FDA) Desk Copy (paper copy only)

/S/ 7/27/98

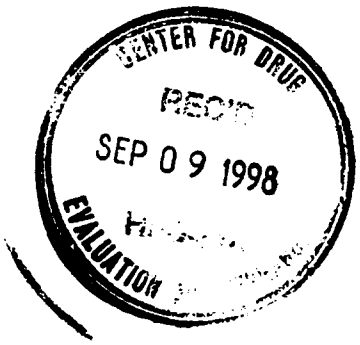
/S/ 7/27/98

/S/ 7/27/98

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



September 8, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Draft Labeling Revision #5 PI
Draft Labeling Revision #3 User

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to a September 3, 1998 facsimile from Ms. Julie Rhee (FDA) to Dr. Kim Birch, Eli Lilly and Company (Lilly) that contained suggested revisions (FDA revisions #5) to the Information for the Physician insert and Information for the User insert for Glucagon for Injection (rDNA origin). We are herewith providing new draft labeling for the Information for the Physician insert (revision #5 PI) and for the Information for the User insert (revision #3 User) that addresses the suggested labeling revisions (Attachments 1 and 2, respectively). Lilly agrees with all of the FDA suggested changes (identified with double underlines) except for the following listed items and proposes alternative wording and/or placement of these phrases as described below. Where Lilly's proposed language differs from that suggested by the FDA, the changes are depicted in a ***different, large, italicized font***. Draft labeling is provided in both paper and electronic format. The diskette has been determined to be free of viruses.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory D Enas

APPEARS THIS WAY
ON ORIGINAL

Gregory Enas, Ph.D.
Director
US Regulatory Affairs

CC: Ms. Julie Rhee (FDA, HFD-510) paper copy and diskette
Dr. Robert Misbin (FDA, HFD-510) Desk Copy (paper copy only)

/S/
8/27/98

Date: August 21, 1998

To: Drs. Fleming/Misbin/Moore/Berlin/Steigerwalt/Rhee/Ahn/Shore

Please take a look at the most recent physician (dated 6/10/98) and patient (dated 7/1/98) package insert and see if you have any additional comments. If you have any comments, please let me know by cob 8/25/98. I checked the labeling against the previous ones and found Lilly has incorporated our comments on these inserts. I also ran these inserts to Mark Askine at DDMAC and attached his comments for your information/inputs.

Physician package insert (dated 6/10/98):

3. PRECAUTIONS section:

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ON ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

June 11, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Draft Labeling Revision #4
(Diskette provided)

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to phone conversations between Ms. Julie Rhee (FDA) and Dr. Kim Birch, Eli Lilly and Company (Lilly) on May 22, 1998 and June 4, 1998 and between Dr. John Holcombe (Lilly) and Dr. Robert Misbin (FDA) on May 20, 1998 regarding draft labeling for NDA 20-928, Glucagon for Injection (rDNA origin). We are herewith providing new draft labeling (revision #4) that addresses the suggested labeling revisions (Attachment 1). All labeling changes are depicted in a ***large bold italicized font*** and are summarized below. Draft labeling is provided in both paper and electronic format. The diskette has been determined to be free of viruses.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory D. Enas

Gregory Enas, Ph.D.
Director
US Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

OK
/S/
6/26/98

Attachment

CC: Dr. Robert Misbin (FDA) Desk Copy (paper copy only)

APPEARS THIS WAY ON ORIGINAL

6/30/98
/S/

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 8-24-98
CSO INITIALS DATE

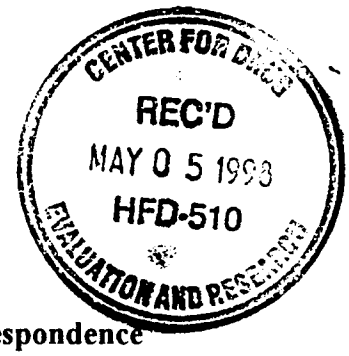
revised and acceptable
/S/
7/1/98

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIG AMENDMENT
BL



May 4, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Draft Labeling Revision #3

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to a Facimile sent from Ms. Julie Rhee (FDA), to Dr. Kim Birch, Eli Lilly and Company (Lilly) on April 22, 1998 that summarized the Pharmacology Reviewer comments for NDA 20-928, Glucagon for Injection (rDNA origin) and suggested changes to the draft physician package insert (Attachment 1). We are herewith providing new draft labeling that addresses the proposed labeling revisions (Attachment 2). In addition we are providing minor changes to the carton labeling (Attachment 3). All labeling changes are depicted in a **different large bold font** and are summarized below. Draft labeling is provided in both paper and electronic format. The diskettes have been determined to be free of viruses.

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acceptable to pharmacol.
/S/
6/1/98

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

for Jennifer L. Stotka, MD
Director
US Regulatory Affairs
Enclosures

paragraph #5 (p#) of the label is ambiguous - can lead to a dangerous delay in a patient getting effective Rx - it is unacceptable - Lilly has been notified about this point previously & I again left a message with Dr Stotka

/S/
5/12/98

CC: Ms. Julie Rhee (FDA) cover letter, diskettes
Dr. Herman Rhee (FDA) Desk Copy (cover letter, document, no disk)
Dr. Robert Misbin (FDA) Desk Copy (cover letter, document, no disk)

Noted
/S/
05 JUN 98

Included in Review
5/20/98
/S/

REVIEWS COMPLETED

CSO ACTION
☐ LETTER MEMO

CSO DATE

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

March 18, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Response to Medical Reviewer

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to a March 2, 1998 facsimile from Ms. Julie Rhee (FDA) to Dr. Kim Birch (Eli Lilly and Company) in which questions were asked concerning the draft labeling of Glucagon for Injection (rDNA origin) (Attachment 1). We are herewith providing a response from Dr. John Holcombe (Attachment 2) and new draft labeling that address issues raised by Dr. Robert Misbin (Attachment 3). All labeling changes are depicted in large underlined font and are summarized below:

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

CC: Dr. Robert Misbin (FDA) Desk Copy

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

March 18, 1998

Robert Misbin, MD

I appreciate the opportunity to respond to your additional comments about rDNA glucagon.

I agree with you that measuring the glucose response to *maximal doses* of animal-sourced and rDNA glucagon does not establish the drugs' bioequivalence. Therefore, in this case the issue is not one of statistical power. We chose the dose of 1 mg Glucagon in study H3F-LC-GFAA because that dose is currently recommended for treating adults with severe hypoglycemia, and our objective was to establish that a dose of 1 mg of rDNA glucagon stimulated an appropriate rise in blood glucose. We chose animal-sourced glucagon as a comparator, since it is the source of drug currently marketed in the United States. While we did not study smaller doses of animal-source and rDNA glucagon given through the subcutaneous and intramuscular routes, doing so may well have established the dose-response relationship, and thus, glucodynamic bioequivalence, for those two sources of glucagon with respect to glucodynamics.

You will note that the proposed labeling for glucagon avoids the term "bioequivalence". Instead, we accurately report the glucodynamic results from study GFAA. That is, "No difference in maximal blood glucose concentration between animal-sourced and rDNA glucagon was observed after subcutaneous and intramuscular injection". Lilly seeks to make no claim as to the bioequivalence of the two products. Instead, we wish simply to point out to physicians that under the conditions studied, ie., 1mg doses given intramuscularly or subcutaneously, we observed no difference in maximum glucose after the injection.

With respect to the proposed package insert language, I want to thank you for your help in continuing to refine the wording. I agree that the proposed wording on page 7, which is essentially unchanged from that in the currently marketed product, could be modified to clarify the appropriate use of glucagon. Certainly, if glucagon and a parenteral form of glucose were both available at the bedside of a patient with severe hypoglycemia, the first choice of therapy should be glucose. Because parenteral glucose is often unavailable to patients with diabetes or to their caregivers, glucagon plays an important role in the treatment of severe hypoglycemia.

To further clarify the appropriate use of glucagon, we have modified the package insert to reflect that the drug should be used as initial therapy to treat severe hypoglycemia only if parenteral glucose can not be used. A copy of the revised package labeling is attached. I believe that you will be pleased with this change.

For your information, I have enclosed two abstracts from the literature, by no means a complete review, but which address the use of glucagon in the emergency treatment of severe hypoglycemia:

Comparison of intravenous glucagon and dextrose in treatment of severe hypoglycemia in an accident and emergency department. Collier A; Steedman DJ; Patrick AW; Nimmo GR; Matthews DM; MacIntyre CC; Little K; Clarke BF. Diabetes Care: 1987, 10 (6) p712. Hypoglycemia is a serious problem in insulin-treated diabetic patients. In this study the efficacy of intravenous glucagon (1 mg) was compared with that of intravenous dextrose (25 g) in the

BEST POSSIBLE COPY

treatment of hypoglycemia in insulin-treated patients attending an accident and emergency department. In addition, the prevailing glycemic control of these patients was compared with patients routinely attending a diabetic outpatient clinic. Both intravenous glucagon and dextrose were effective in the treatment of hypoglycemic coma. There was a difference in the glycemic profile after intravenous glucagon compared with intravenous dextrose, and recovery of a normal level of consciousness after glucagon was slower than after dextrose (6.5 vs. 4.0 min, respectively; P less than .001), although the average duration of hypoglycemic coma was 1.4 h. The glucagon- and dextrose-treated groups had significantly lower HbA1 than comparable patients routinely attending the clinic (9.5 +/- 0.8 vs. 12.0 +/- 3.8%, respectively; P less than .001). In view of the ease of administration and the small risk of vascular and extravascular complications, intravenous glucagon appears to be a useful alternative to intravenous dextrose in the treatment of severe hypoglycemia.

Glucagon: prehospital therapy for hypoglycemia. Vukmir RB; Paris PM; Yealy DM. Ann Emerg Med. 1991, 20 (4) p375-9
STUDY OBJECTIVE: This study evaluated the efficacy of glucagon for prehospital therapy of hypoglycemia in patients without IV access. DESIGN: Prospective clinical trial. SETTING: Prehospital in a busy, urban emergency medical services system. TYPE OF PARTICIPANTS: Fifty consecutive patients presenting with documented hypoglycemia (ChemStrip BG less than or equal to 80 mg/dL) and symptoms of decreased level of consciousness, syncope, or seizure were enrolled. MEASURES AND MAIN RESULTS: Data collected included pretreatment (ChemStrip BG) and post-treatment serum glucose (hospital assay) as well as assessment of level of consciousness by a quantitative measure, the Glasgow Coma Score, and by a qualitative scale (0 to 3). The mean pretreatment blood glucose of 33.2 +/- 23.3 mg/dL increased after treatment to 133.3 +/- 57.3 mg/dL. Qualitative level of consciousness increased from a mean of 1.26 +/- .96 to 2.42 +/- .94 and Glasgow Coma Score increased from a mean of 9.0 +/- 4.19 to 13.04 +/- 3.68. The mean time until response was 8.8 minutes in those who responded to both level of consciousness criteria 82% (41 of 50). Glucagon administered for hypoglycemia resulted in a glucose increase in 98% (49 of 50) with headache as the only side effect noted in 4% (two of 50) of patients (P less than .0001). CONCLUSION: Glucagon is safe and effective therapy for hypoglycemia in the prehospital setting.

Thank you again for your suggestions and your cooperation.

Respectfully submitted,

for Lynn Birch

John H. Holcombe, MD
Senior Clinical Research Physician
Eli Lilly and Company

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ON ORIGINAL

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Lilly's revision #1

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 25 1998
HFD-510

February 16, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Response to Medical Reviewer

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to a February 3, 1998 facsimile from Ms. Julie Rhee (FDA) to Dr. Kim Birch (Eli Lilly and Company) in which labeling suggestions were provided for our consideration and questions were asked concerning glucagon antibodies and E. coli polypeptide antibodies (Attachment 1). We are herewith providing new draft labeling that address the proposed labeling suggestions as well as minor editorial changes (Attachment 2) and our response to the antibody questions. All labeling changes are depicted in large font.

APPEARS THIS WAY
ON ORIGINAL

2 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

/s/ J L Stotka

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

/S/ 3-24-98

CSO INITIALS DATE

CC: Dr. Robert Misbin (FDA) Desk Copy

MOR comments (dated 4/27/98) faxed to the sponsor on 3/2/98.

Nadine 3/25/98 /S/

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 20, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

NEW CORRESP

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made phone conversations between Ms. Julie Rhee (FDA) and Dr. Kim Birch, Eli Lilly and Company (Lilly) on August 11, 1998 regarding the lack of a signature block on the patent certification statement submitted to NDA 20-928. We are herewith providing an updated patent information statement with signature.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory D Enas

Gregory Enas, Ph.D.
Director
U.S. Regulatory Affairs

Enclosures

CC: Ms. Julie Rhee (FDA, HFD-510) desk copy

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

GLUCAGON FOR INJECTION (rDNA origin)

NDA 20-928

ITEM 13. PATENT INFORMATION

The undersigned declares that there are no patents covering the product which is the subject of this New Drug Application.

Eli Lilly and Company

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs

GLUCAGON FOR INJECTION (rDNA origin)

NDA 20-928

ITEM 13: PATENT INFORMATION

The undersigned declares that there are no patents covering the product which is the subject of this New Drug Application.

ITEM 14: PATENT CERTIFICATION

Eli Lilly and Company (Lilly) claims a five year period of exclusivity for the use of r-glucagon as provided by 21 C.F.R. 314.108(b)(2). As evidenced by the absence in the Orange Book that r-glucagon has previously been approved by the FDA, to the best of Applicant's knowledge and belief, r-glucagon has not previously been approved under section 505(b) of the FFDCA. Accordingly, Lilly submits r-glucagon as a new chemical entity entitled to a five year period of exclusivity as provided by FFDCA 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii) (21 U.S.C. 355(c)(3)(D)(ii) and 355(j)(4)(D)(ii)).

EXCLUSIVITY SUMMARY for NDA # 20-928 SUPPL # ____

Trade Name Glucagon (rDNA origin) for Injection Generic Name _____

Applicant Name Eli Lilly HFD-510

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO /_X_/ *

   * The NDA includes PK/PD bioequivalence studies comparing to their animal-sourced glucagon (NDA 12-122) and a safety study.

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

___5 years_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /_X__/ NO /___/

If yes, NDA # _20-918_____ Drug Name _Glucagon_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ___ YES /___/ ! NO /___/ Explain: ____

! _____

Investigation #2 !

IND # ___ YES /___/ ! NO /___/ Explain: ____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/ 8-26-98

Signature Date

Title: Project Manager

/S/ 9/10/98

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

/BLA # 20-928 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-510 Trade and generic names/dosage form: Glucagon (rDNA) Inj Action: (AP) AE NA

Applicant Eli Lilly Therapeutic Class 3P

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application Treatment of severe hypoglycemia/diagnostic aid

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ✓ Children (2-12yrs) ✓ Adolecents(12-16yrs)

✓ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/ 12/22/98

Signature of Preparer and Title Date

Orig NDA/BLA # 20-928

HFD-510 /Div File

NDA/BLA Action Package

HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Debarment Certification

NDA Application No.: 20-928

Drug Name: **Glucagon for Injection (rDNA origin)**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Jennifer L. Stotka, M.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Jennifer L. Stotka, M.D.

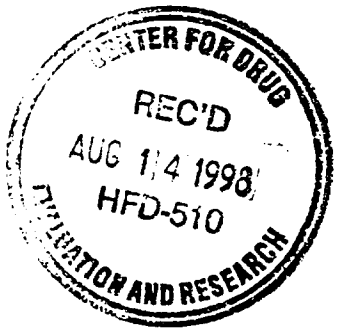
Title: Director, U.S. Regulatory Affairs

Date: December 10, 1997

Lilly ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIG AMENDMENT



August 13, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

Safety Update

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to the submission (December 11, 1998) of a New Drug Application (NDA) for Glucagon for Injection (rDNA origin).

Per an August 12,1998 phone conversation between Ms. Julie Rhee (Food and Drug Administration) and Dr. Kim Birch (Eli Lilly and Company) and per the requirements of 21 CFR §314.50(d)(5)(vi)(b) we are herewith submitting the requested safety update. No new safety information in animals or humans is available for rGlucagon. All patients enrolled in the rGlucagon clinical trials completed the study and follow-up at the time of NDA submission and no additional animal studies have been performed. For safety information on animal-source glucagon, please refer to the NDA annual report for animal glucagon that was submitted on February 2, 1998 to NDA 12-122.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

LAJ

/S/

8/26/98

ELI LILLY AND COMPANY

Gregory Enas, Ph.D.
Director
US Regulatory Affairs

CC: Ms. Julie Rhee (FDA, HFD-510)
Dr. Robert Misbin (FDA, HFD-510)

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☑ N.A.I. ☐ MEMO	8-26-98
CSO INITIALS	DATE

ORIGINAL

BM

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

CENTER FOR DRUG
REC'D
APR 14 1998
HFD-510
EVALUATION AND RESEARCH

April 13, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room, 14B-14
5600 Fishers Lane
Rockville, MD 20857-1706

4-Month Safety Update

Voted
/S/
4/14/98

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to the submission (December 11, 1998) of a New Drug Application (NDA) for Glucagon for Injection (rDNA origin).

Per the requirements of 21 CFR §314.50(d)(5)(vi)(b) we are herewith submitting the requisite 4-month safety update. No new safety information in animals or humans is available for rGlucagon. All patients enrolled in the rGlucagon clinical trials completed the study and follow-up at the time of NDA submission and no additional animal studies have been performed. For safety information on animal-source glucagon, please refer to the NDA annual report for animal glucagon that was submitted on February 2, 1998 to NDA 12-122.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
US Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

/S/ 4-22-98
CSO INITIALS DATE

CC: Julie Rhee (FDA)
Robert Misbin (FDA)

RHEE

JAN 8 1997

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 7, 1998

From: Mathematical Statistician (HFD-715)

Through: Ed Nevius, Ph.D.
Director of Division of Biometrics 2
(HFD-715)

Subject: Statistical review not needed

To: File (NDA 20-928)

I have reviewed the documents submitted for NDA 20-928 (Glucagon). The studies presented to establish efficacy are PK/PD bioequivalence studies that do not require statistical input and therefore a review is not needed for this NDA.

/S/

Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius /S/ 1-8-97

cc:
Orig. NDA 20-928
HFD-510
HFD-510/JRhee, RMisban, HAhn
HFD-715/DOB 2 File, Chron, ENevius, JMele

Mele/827-6376/DOB2/WordPerfect-glucagon.mem/Jan 7, 1998

This memorandum contains 1 page.

Memorandum of Telecon

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date of Telecon:	01/07/98
From:	Robert M. Shore, Pharm.D. /S/ JAN - 7 1998
Re:	NDA 20-928/N-000 rGlucagon Lilly
Participants:	Robert M. Shore (FDA); Jim Woodworth (Lilly)

Jim Woodworth called yesterday, 01/06/98, to explain why there are discrepancies between the IND and NDA bioequivalence data (see teleconference memo 01/05/98). Jim called back today to add further explanation. He stated that, in the IND, only mean log-transformed data was used to generate 90% confidence interval estimates for the assessment of bioequivalence. In the NDA, a more complete ANOVA was used which included period and sequence effects and generated least squared means which were used for the 90% confidence interval estimates. This, he stated, explains why the IND results are different from the NDA results. Indeed, I told him that one of my comments on the IND review was about the lack of information on the statistical model, if any, that was used to calculate bioequivalence parameters.

CC: NDA 20-928/N-000 (orig., 1 copy), HFD-510(Misbin, RheeJ), HFD-870 (Ahn, ChenME, Shore)

APPEARS THIS WAY
ON ORIGINAL

RHEE

Memorandum of Telecon

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date of Telecon:	01/06/98
From:	Robert M. Shore, Pharm.D. /S/
Re:	NDA 20-928/N-000 rGlucagon Lilly
Participants:	Robert M. Shore (FDA); Jim Woodworth (Lilly)

JAN - 7 1998

Jim Woodworth called to explain why there are discrepancies between the IND and NDA bioequivalence data (response to Teleconference on 01/05/98). Jim stated that the IND preliminary report was just that - a 'preliminary report'. When it was generated, the actual blood collection times for every individual were not known; therefore, some nominal (scheduled) collection times were used to calculate pharmacokinetic parameters. With the NDA, actual collection times are used in all individuals.

In follow-up, I spot-checked some glucagon AUC calculations using the actual collection times; the results support this explanation.

CC: NDA 20-928/N-000 (orig., 1 copy), HFD-510(Misbin, RheeJ), HFD-870 (Ahn, ChenME, Shore)

APPEARS THIS WAY
ON ORIGINAL

RHEE

Memorandum of Telecon

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

JAN - 5 1998

Date of Telecon:	01/05/98
From:	Robert M. Shore, Pharm.D. /S/
Re:	NDA 20-928/N-000 rGlucagon Lilly
Participants:	Robert M. Shore (FDA); Kim Birch (Lilly)

Kim Birch (317-277-1443) returned my call. I pointed out to her that there are discrepancies between the IND bioequivalence data (IND 51,559/N-012 cover letter 04/28/97) and the NDA data for the different rGlucagon formulations. The example I gave was summary tables for 90% confidence intervals (page 2109-2110 of the IND and V1.21, p 105 of the NDA). Although the ratios reported in the NDA are inverted from those reported in the IND, this does not account for the discrepancy. Indeed, even individual pharmacokinetic parameters appear to differ between the submissions.

Kim stated that she would contact Jim Woodworth and he may contact me directly.

CC: NDA 20-928/N-000 (orig., 1 copy), HFD-510(Misbin, RheeJ), HFD-870 (Ahn, ChenME, Shore)

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 11, 1998

APPLICATION NUMBER: 20-928; Glucagon (rDNA) for Injection

BETWEEN:

Name: Mary Ann Holovac, HFD-
(301) 827-5470

AND

Name: Julie Rhee, HFD-510

SUBJECT: Exclusivity

I called Mary Ann to inquire about an exclusivity of this NDA. I mentioned that this NDA was submitted as 505(b)(1) and the sponsor had conducted bioequivalence studies plus a small safety study. I asked Mary Ann if a safety study qualifies for an exclusivity. Mary Ann told me usually a safety study does not qualify for an exclusivity and they (including generic) will decide whether or not this NDA qualifies for an exclusivity.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

/S/

Julie Rhee

cc: Original 20-928
HFD-510/Div. File
HFD-510/Julie Rhee

APPEARS THIS WAY
ON ORIGINAL

TELECON

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: August 19, 1998
Background: The animal-sourced glucagon (NDA 12-122) had a separate patients package insert for (1) diagnostic use, and (2) emergency use kit. However, this NDA contains a single patients package insert. I called Dr. Birch and mentioned that only one patients package insert was submitted in this NDA and asked if this insert is for diagnostic use, or for emergency use. Dr, Birch informed me that since patients package insert for diagnostic use, and emergency use are the same, they decided to go with a single patients package insert. cc:OrigNDA HFD-510/DivFile HFD-510/Misbin/HRhee/Berlin APPEARS THIS WAY ON ORIGINAL APPEARS THIS WAY ON ORIGINAL /S/ **Name: Julie Rhee**	**NDA#:** 20-928 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Glucagon (rDNA origin) for Injection **Firm Name:** Eli Lilly **Name and Title of Person with whom conversation was held:** Kim Birch, Ph.D. Regulatory Affairs **Phone:** (317) 277-1443 APPEARS THIS WAY ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** August 12, 1998
I called Dr. Birch and requested the following: 1. Since the last safety update was submitted in 4/98, another safety update submission is needed. 2. On 6/6/98 submission: a clarification is needed for "sufficient" for item #6, under drug substance, and item #1, under drug product. They can clarify "sufficient" in terms of the number of batches or in terms of months or years. Dr. Birch agreed to submit a safety update before the end of this week. APPEARS THIS WAY ON ORIGINAL cc:OrigNDA HFD-510/DivFile HFD-510/Misbin/Berlin APPEARS THIS WAY ON ORIGINAL /S/ --- **Name: Julie Rhee**	**NDA#:** 20-928 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Glucagon **Firm Name:** Eli Lilly **Name and Title of Person with whom conversation was held:** Kim Birch, Ph.D. Regulatory Affairs **Phone:** (317) 277-1443 APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-928

JUN 11 1998

Eli Lilly and Company
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

We acknowledge receipt on June 9, 1998, of your June 8, 1998, amendment to your new drug application for Glucagon (rDNA origin) for Injection.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is September 12, 1998.

If you have any questions, please contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: June 5, 1998
Submission date: 12/11/97, 1/16 and 4/5/98 When Dr. Birch returned my call, I informed her that on 5/4/98 labeling amendment, page 3, Figure 1, the number of normal volunteers should be changed from 29 to 25 because the number of subjects that completed the 1 mg SQ treatment with the rDNA glucagon pH=2.0 was 25. She said she will verify the number and submit a revised labeling. She also mentioned that a major CMC amendment will be submitted on Monday (June 8) by over night express. I asked her to include a desk copy. She agreed. cc:OrigIND HFD-510/DivFile HFD-870/Shore HFD-510/Berlin /S/ --- **Name: Julie Rhee**	**NDA#:** 20-928 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Glucagon (rDNA) **Firm Name:** Eli Lilly **Name and Title of Person with whom conversation was held:** Kim Birch, Ph.D. Regulatory Affairs **Phone:** (317) 277-1443

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: May 26, 1998
Re: Our 5/20/98 CMC fax to Lilly Dr. Berlin and I called Dr. Birch to discuss Lilly's response to our 5/20/98 CMC fax. Dr. Birch assured us that we could expect their response to our fax no later than June 8. I informed Dr. Birch that their response will constitute as a major amendment and will extend the review clock by 90-days. She said she understood. Dr. Berlin informed her that he was informed by compliance the acceptable EER report could be expected by the end of this week. I asked Dr. Birch to wait for biopharm labeling comments before they submit a labeling amendment. She agreed. cc:OrigNDA 20-928 HFD-510/DivFile HFD-510/Berlin APPEARS THIS WAY ON ORIGINAL APPEARS THIS WAY ON ORIGINAL /S/ --- **Name: Julie Rhee**	**NDA#:** 20-928 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Glucagon (rDNA origin) for Injection **Firm Name:** Eli Lilly **Name and Title of Person with whom conversation was held:** Kim Birch, Ph.D. Regulatory Affairs **Phone:** (317) 277-1443 APPEARS THIS WAY ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** May 22, 1998
Re: May 4, 1998 submission I called Dr. Birch and requested to substitute ". . . a slight . . " with ". . . an . . . ' under the *Carcinogenesis, Mutagenesis, Impairment of Fertility* section. Dr. Birch agreed to make the change in their labeling revision #4. APPEARS THIS WAY ON ORIGINAL cc:OrigNDA HFD-510/DivFile HFD-510/Steigerwalt/HRhee APPEARS THIS WAY ON ORIGINAL --- **Name: Julie Rhee**	**NDA#:** 20-928 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Glucagon (rDNA) for Injection **Firm Name:** Eli Lilly **Name and Title of Person with whom conversation was held:** Kim Birch, Ph.D. Regulatory affairs **Phone:** (317) 277-1443 APPEARS THIS WAY ON ORIGINAL

Rhee

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** May 21, 1998
Re: Our fax dated 5/20/98 I called Dr. Birch and informed her that there was a typo on our 5/20/98 fax on CMC review comments. I informed her that under the "Labeling" Dr. Birch mentioned that they had caught the mistake. However, since this product has more than one pharmacological class (i.e., anti-hypoglycemic and smooth muscle relaxer), she wanted Drs. Misbin, Berlin, and Moore discuss how to handle it. I told her I'll look into it. APPEARS THIS WAY ON ORIGINAL cc:OrigNDA HFD-510/DivFile HFD-510/Berlin/Moore APPEARS THIS WAY ON ORIGINAL /S/ **Name: Julie Rhee**	**NDA#:** 20-928 **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Glucagon (rDNA origin) for Injection **Firm Name:** Eli Lilly **Name and Title of Person with whom conversation was held:** Kim Birch, Ph.D. Regulatory Affairs **Phone:** (317) 277-1443 APPEARS THIS WAY ON ORIGINAL

NDA 20-928

JAN 23 1998

Eli Lilly and Company
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

Please refer to your December 11, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucagon (rDNA origin) for Injection.

We also refer to our acknowledgement letter dated December 18, 1997, which stated that the therapeutic drug review classification for this application would be decided at the filing meeting.

Our policy regarding determination of priority or standard review status is based on the proposed indications and alternate treatment(s) marketed for the proposed indication. Upon further consideration of your application, we have concluded that this application should receive a priority review.

If you have any questions, please contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

/S/ 1-23-98

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-928

DEC 18 1997

Eli Lilly and Company
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Glucagon for Injection (rDNA origin)

Therapeutic Classification: To be decided at filing meeting

Date of Application: December 11, 1997

Date of Receipt: December 12, 1997

APPEARS THIS WAY
ON ORIGINAL

Our Reference Number: 20-928

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 10, 1998, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ 12/18/97

APPEARS THIS WAY
ON ORIGINAL

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Lilly ORIGINAL BC

ORIG AMENDMENT

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

CENTER FOR DRUG
REC'D
AUG 19 1998
HFD-510
EVALUATION AND RESEARCH

August 18, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-928, Amendment, Vials Glucagon for Injection (rDNA origin)

This amendment provides additional details for the responses to two chemistry, manufacturing, and control questions submitted June 8, 1998.

Please call Ms. Ann Maloney at (317) 276-0156 or me at (317) 276-0368 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Tobias Massa, Ph.D.
Director
Regulatory Affairs (Chemistry, Manufacturing, and Control)

8/27/98

enclosure

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☑ N.A.I. ☐ MEMO
8-27-98 DATE
CSO INITIALS

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

June 18, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT
Replacement of
Missing Pages

Re: NDA 20-928, Glucagon for Injection (rDNA origin)

We are herewith submitting 6 pages to NDA 20-928 that were inadvertently left out of the original submission. This information describes the methods for the glucagon radioimmunoassay used to measure glucagon levels in human plasma. This information was sent via facsimile from Dr. Kim Birch (Eli Lilly and Company) to Mr. Robert Shore (FDA) on June 16, 1998 as requested. A 1-page "place-holder" titled "Appendix A. Method ICD 32" can be found in NDA 20-928, volume 1-22, page 200. This information should follow this place-holder. We apologize for any inconvenience this may have caused.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory Enas, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure
CC: Ms. Julie Rhee (FDA, HFD-510)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

June 11, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Draft Labeling Revision #4
(Diskette provided)

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to phone conversations between Ms. Julie Rhee (FDA) and Dr. Kim Birch, Eli Lilly and Company (Lilly) on May 22, 1998 and June 4, 1998 and between Dr. John Holcombe (Lilly) and Dr. Robert Misbin (FDA) on May 20, 1998 regarding draft labeling for NDA 20-928, Glucagon for Injection (rDNA origin). We are herewith providing new draft labeling (revision #4) that addresses the suggested labeling revisions (Attachment 1). All labeling changes are depicted in a ***large bold italicized font*** and are summarized below. Draft labeling is provided in both paper and electronic format. The diskette has been determined to be free of viruses.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-4038 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory D. Enas

Gregory Enas, Ph.D.
Director
US Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Attachment

CC: Dr. Robert Misbin (FDA) Desk Copy (paper copy only)

APPEARS THIS WAY
ON ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIGINAL

ORIG AMENDMENT

June 8, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-928, Amendment, Vials Glucagon for Injection (rDNA origin)

This amendment provides responses to the chemistry, manufacturing, and control questions received by fax on May 20, 1998.

Please call Ms. Ann Maloney at (317) 276-0156 or me at (317) 276-0368 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

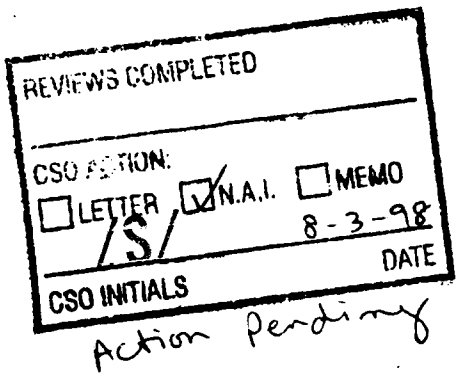
Sincerely,

ELI LILLY AND COMPANY

Tobias Massa, Ph.D.
Director
Regulatory Affairs (Chemistry, Manufacturing, and Control)

enclosure

desk copy: Ms. Julie Rhee



Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

DRUG AMENDMENT
BL

May 4, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence
Draft Labeling Revision #3

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to a Facimile sent from Ms. Julie Rhee (FDA), to Dr. Kim Birch, Eli Lilly and Company (Lilly) on April 22, 1998 that summarized the Pharmacology Reviewer comments for NDA 20-928, Glucagon for Injection (rDNA origin) and suggested changes to the draft physician package insert (Attachment 1). We are herewith providing new draft labeling that addresses the proposed labeling revisions (Attachment 2). In addition we are providing minor changes to the carton labeling (Attachment 3). All labeling changes are depicted in a **different large bold font** and are summarized below. Draft labeling is provided in both paper and electronic format. The diskettes have been determined to be free of viruses.

DUPLICATE

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

for Jennifer L. Stotka, MD
Director
US Regulatory Affairs
Enclosures

APPEARS THIS WAY
ON ORIGINAL

CC: Ms. Julie Rhee (FDA) cover letter, diskettes
Dr. Herman Rhee (FDA) Desk Copy (cover letter, document, no disk)
Dr. Robert Misbin (FDA) Desk Copy (cover letter, document, no disk)

APPEARS THIS WAY
ON ORIGINAL

ORIG AMENDMENT ORIGINAL

PSI

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

February 13, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-928, Amendment, Vials Glucagon for Injection (rDNA origin)

This amendment provides the responses to the microbiology questions received on February 4, 1998.

Please call Ms. Ann Maloney at (317) 276-0156 or me at (317) 276-0368 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Tobias Massa

Tobias Massa, Ph.D.
Director
Regulatory Affairs (Chemistry, Manufacturing, and Control)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

/S/ 4-14-98
CSO INITIALS DATE

Micro consult was sent & the review has been completed.

noted /S/ 4/13/98

enclosure

desk copy: Dr. William Berlin

Noted 3/11/98 /S/

NEW CORRESP ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 2 8 1998
HFD-510

January 27, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

Correspondence

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Reference is made to a phone conversation between Dr. Herman Rhee, FDA Pharmacologist and Dr. Kim Birch, Eli Lilly and Company (Lilly) on January 13, 1998 in which Dr. Rhee requested information on the cardiovascular effects (e.g. heart rate, blood pressure, and inotropic effects) of recombinant glucagon observed in animal (dog) and human studies and a comparison of this information to known cardiovascular effects of Lilly's We are herewith providing a summary of the nonclinical cardiovascular pharmacology studies with recombinant glucagon and a discussion of the cardiovascular effects observed with Lilly's animal-derived glucagon published in the literature (Attachment 1). In addition, we include a summary of the cardiovascular effects of glucagon in humans. Specifically, observations from Lilly clinical trials, one of which compares animal-derived glucagon directly to recombinant glucagon, are discussed (Attachment 2).

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

/S/ 4/13/98

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
/S/ 4/13/98

CSO INITIALS DATE

/S/ 4/14

/S/ 3/11/98

CC: Dr. Herman Rhee (FDA) Desk Copy
Dr. Robert Misbin (FDA) Desk Copy

/S/ 3/11/98

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

January 26, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Dr. Solomon Sobel
5600 Fishers Lane
Rockville, MD 20857-1706

CORRESPONDENCE

noted
/S/
3/11/98

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Eli Lilly and Company (Lilly) would like to thank you for recognizing the importance of Glucagon for Injection (rDNA origin) by assigning the NDA a Priority Review. The ability to offer patients a reliable supply of glucagon that is independent of the use of animal glands is a high priority for the company. Plans to shutdown and demolish our animal insulin/glucagon manufacturing facility has been expedited and aggressive target dates set for the opening of our new recombinant DNA manufacturing facility following news of the Priority rating. When we begin the transition from the old to the new facility and from animal-derived to recombinant DNA-derived manufacturing processes, Lilly intends to exhaust supplies of animal glucagon prior to launching our recombinant glucagon product. The goal of this strategy is to minimize the likelihood of a shortage of this critical care product in the market. Again, Lilly thanks you for acknowledging the significant benefits to patients that recombinant glucagon offers.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☑ N.A.I. ☐ MEMO	
/S/	3-18-98
CSO INITIALS	DATE

noted
/S/
1/29/98

CC: Dr. Alexander Fleming (FDA)
Dr. Robert Misbin (FDA)

noted
3/11/98
/S/

ORIG AMENDMENT

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

January 16, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-928, Amendment, Vials Glucagon for Injection (rDNA origin)

This amendment provides the responses to the biopharm questions received on January 13, 1998.

Please call Ms. Ann Maloney at (317) 276-0156 or me at (317) 276-4125 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

/S/ 4-6-98
CSO INITIALS DATE

Sincerely,

ELI LILLY AND COMPANY

Gregory C. Davis

Gregory C. Davis, Ph.D.
Director
Regulatory Affairs (Chemistry, Manufacturing, and Control)

/S/ 7apr98

1/20/98

enclosure

/S/

desk copy: Dr. William Berlin

/S/ 3/11/98

/S/

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

January 8, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee (desk copy)
5600 Fishers Lane
Rockville, MD 20857-1706

CORRESPONDENCE

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Per your request we are providing you with an electronic copy of the Information for the Physician and Information for the Patient draft package inserts for Glucagon for Injection (rDNA origin) that were included in NDA 20-928. Both inserts are in Microsoft Word format and are provided on a diskette that has been verified to be free of viruses.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

/S/ 8-24-98
CSO INITIALS DATE

enclosure

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

January 6, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

CORRESPONDENCE
CORRECTION

Re: NDA 20-928; Glucagon for Injection (rDNA origin)

Please disregard the correspondence dated December 12, 1997 that was submitted to NDA 20-928 in error. We apologize for any inconvenience this may have caused you.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

APPEARS THIS WAY
ON ORIGINAL

Jennifer L. Stotka, MD
Director
US Regulatory Affairs

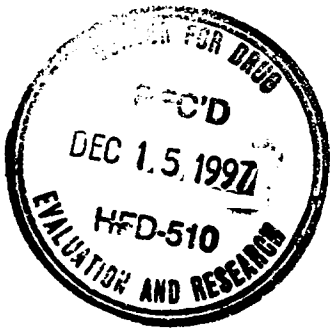
cc: Ms. Julie Rhee (FDA)

ORIG AMENDMENT ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



December 12, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

CORRESPONDENCE

Re: NDA 20-928; Glucagon for Injection (rDNA origin) - Electronic Media

The enclosed materials were omitted inadvertently from yesterday's submission. We apologize for any inconvenience. This packet contains information specifically requested to be delivered to Dr. Robert Shore. It provides a compilation of background information and rationale for a priority rating, as well as previous correspondence and slides from the pre-NDA meeting in March of 1997, and information on Lilly study H3F-LC-GFAA.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Reviewing Desk Copy
/S/
12/19/97

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

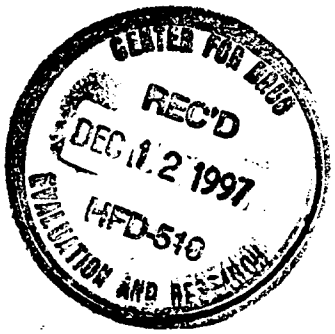
enclosures

cc: Dr. Robert Shore (FDA, HFD-870)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



December 11, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Ms. Julie Rhee
5600 Fishers Lane
Rockville, MD 20857-1706

CORRESPONDENCE

Re: NDA 20-928; Glucagon for Injection (rDNA origin) - Electronic Media

Eli Lilly and Company (Lilly) is herewith submitting a single CD-ROM disk that contains an identical electronic copy of items 1, 2, 3, 6, 8, 10, 11 and 12 from the Glucagon for Injection (rDNA origin) NDA. All files on the CD-ROM disk are in Adobe PDF format. Please note that the case report tabulations and case report forms, usually included in items 11 and 12 respectively, are included as part of the clinical study reports located in items 6 and 8. Two diskettes containing Part 1 and Part 2, respectively of the pharmacokinetic and pharmacodynamic datasets and output files from study GFAA (NDA Item 6) are included in three formats (".txt" = tab-delimited ASCI files, ".prn" = space-delimited ASCI files, and ".xls" = Excel files) for use by the Biopharmaceutics group as requested. We are also including three additional copies of NDA Volume 1.1 as requested.

If you have any questions concerning the functionality of the CD-ROM, please contact:

Steven T. Ward
(317) 276-2952 (work)
(317) 256-8888 (pager)

If you have any questions concerning the functionality of the electronic media containing the pharmacokinetic and pharmacodynamic datasets, please contact:

Dr. Jim Woodworth
(317) 276-1304 (work)

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
U.S. Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

enclosures

CC: Cover letter to:
Dr. Robert Shore (FDA, HFD-870)

APPEARS THIS WAY
ON ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

December 11, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

NEW DRUG APPLICATION

Re: NDA 20-928—Glucagon for Injection (rDNA origin)

This letter accompanies the submission by Eli Lilly and Company (Lilly) of an original New Drug Application (NDA) for Glucagon for Injection (rDNA origin) [referred to as rGlucagon] to support the indications for the treatment of hypoglycemia and for use as a diagnostic aid for radiologic examinations. Currently, animal-derived Glucagon for Injection is approved for these indications.

This 38 volume NDA contains clinical data from two clinical studies; a pharmacokinetic/pharmacodynamic study in healthy volunteers that used animal-derived glucagon as the comparator (GFAA) and a safety study in healthy volunteers that measured rGlucagon stimulated antibody formation (immunogenicity) compared with animal-derived glucagon (GFAB).

Lilly believes that the NDA for Glucagon for Injection (rDNA origin) warrants an expedited review. The rationale for this conclusion is described in the Regulatory Background Information section located in the first volume.

Lilly has discussed the registration plans for rGlucagon with the FDA personnel. These meetings and communications have been summarized in the Regulatory Background Information section of this application included in volume 1. The understandings and agreements reached between Lilly and the FDA have been incorporated into this application.

This application is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" and the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications". An identical electronic copy of items 1, 2, 3, 6, 8, 10, 11 and 12 has been provided on a single CD-ROM disk. All files on the CD-ROM disk are in Adobe PDF format. A diskette containing the pharmacokinetic and pharmacodynamic datasets and output files will be provided to the Biopharmaceutics group as requested.

All electronic media have been checked by Lilly Information Technology personnel and have been verified to be free of known viruses.

As required by regulations, we hereby certify that the field copy is being provided simultaneously to our home FDA district office in Detroit, Michigan and that this copy contains all appropriate sections, identical to those provided to the reviewing division. Lilly affirms that all manufacturing sites listed in this application that are involved in the manufacturing, packaging and labeling of Glucagon for Injection (rDNA origin) are available for pre-approval inspection.

The initial User Fee for this submission has been paid under User Fee This fee amount was determined using the fee structure for fiscal year 1997 under PDUFA 1 as recommended by Mr. Tom Hassel (FDA) in a phone conversation with Dr. Kim Birch (Lilly) on November 17, 1997 with the understanding that the remainder of the User Fee will be billed according to PDUFA 2 fee structure at a later time. Form 3397 is provided.

A Debarment Certification has been provided.

To facilitate the review of this application, we suggest that any facsimile (FAX) or other written communication, regardless of subject, be directed to:

Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FAX number (317) 276-1652

Telephone calls should be made between the hours of 7:30 a.m. and 4:15 p.m. (EST). Any calls concerning general issues, clinical reports and labeling should be made to:

Kim Birch, Ph.D.
(317) 277-1443 (work)
(317) 256-6033 (pager)
(317) 834-2743 (home)

or alternatively you may reach Dr. Birch via E-mail at Kbirch@Lilly.com

In case of Dr. Birch's absence please contact:

Jennifer L. Stotka, M.D.
(317) 276-1249 (work)
(317) 257-7606 (home)

Any telephone calls related to manufacturing and control issues should be made to:

Gregory Davis, Ph.D.
(317) 276-4125 (work)
(317) 581-9101 (home)

or in his absence to:

Ann Maloney
(317) 276-0156 (work)
(317) 259-1198 (home)

Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Philip R. Reid, M.S.

APPEARS THIS WAY
ON ORIGINAL

Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs

Enclosures

cc: **Desk copies**: Cover Letter and Regulatory Background Information only to:

Dr. Hae-Young Ahn (HFD-870)
Dr. James Bilstad (HFD-102)
Dr. G. Alexander Fleming (HFD-510)
Ms. Enid Galliers (HFD-511)
Dr. Robert Misbin (HFD-510)
Dr. Stephen Moore (HFD-510)
Ms. Julie Rhee (HFD-510)
Dr. Robert Shore (HFD-870)
Dr. Solomon Sobel (HFD-510)

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SUMMARY OF INDEX