CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020918

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

J. Phee

JUN 7 0 1999

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-918/N-000	**SUBMISSION DATE:**	**26-MAY-98**
BRAND NAME:	**GlucaGen®**	
GENERIC NAME:	**glucagon (rDNA) 1mg for injection**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Novo Nordisk Pharmaceuticals, Inc., Princeton, NJ**	
TYPE OF SUBMISSION:	**BB: Study Report**	

TERMS AND ABBREVIATIONS:

AUCa-b ..... Area under the plasma-concentration-time curve from time a to time b
DMEDP ..... Division of Metabolic and Endocrine Drug Products
(b)(4)
IM ..... Intramuscular
OCPB .. .. Office of Clinical Pharmacology and Biopharmaceutics
rDNA ..... Recombinant DNA
(b)(4)
SC ..... Subcutaneous

SYNOPSIS:

APPEARS THIS WAY ON ORIGINAL

Results from study 007 fulfill the requirement, in 21CRF320.21(a)(1), to demonstrate in vivo bioavailability of a drug product that is the subject of an NDA.

RECOMMENDATION:

APPEARS THIS WAY ON ORIGINAL

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 20-918 submitted 26-MAY-98. The overall Human Pharmacokinetic Section is acceptable to OCPB. This recommendation, comments (p. 4), and labeling comments (p. 4) should be sent to the sponsor as appropriate.

APPEARS THIS WAY ON ORIGINAL

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

BACKGROUND: APPEARS THIS WAY ON ORIGINAL

Currently, glucagon is only available from animal sources. Novo Nordisk proposed to market a recombinant DNA glucagon. Previous submissions were deemed not approvable by OCPB due to unreliable RIA assays for glucagon in plasma. Therapeutic equivalence between the marketed animal-source glucagon and GlucaGen has already been demonstrated (Study 006 submitted 18-SEP-98). The current submission contains data from a bioavailability study of GlucaGen which was undertaken to fulfill 21CRF320.21(a)(1) which requires evidence demonstrating in vivo bioavailability of a drug product which is the subject of an NDA. APPEARS THIS WAY ON ORIGINAL

PROTOCOL INDEX

Protocol Number	Title	Page
Glu/USA/007/USA	Pharmacokinetic assessment of glucagon after intramuscular injection.	p. 6

DRUG FORMULATION: APPEARS THIS WAY ON ORIGINAL

This submission indicated that the formulation used in the bioavailability study Glu/USA/007/USA was from a (b)(4)

ANALYTICAL METHODOLOGY: APPEARS THIS WAY ON ORIGINAL

Since the (b)(4) used for detection of glucagon in human plasma samples has been a major problem in previous submissions, John Strong (Office of Testing and Research/ Laboratory of Clinical Pharmacology) was asked to review the current assay. His review can be found in Appendix 2 and indicated

My conclusions are that the Sponsor has documented that dilution of

sample to achieve concentrations within (b)(4) is valid and that the method should produce reliable human plasma glucagon concentrations.

APPEARS THIS WAY ON ORIGINAL

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

APPEARS THIS WAY ON ORIGINAL

A. Relative Bioavailability

Study Glu/USA/007/USA was a single-dose in vivo bioavailability study of GlucaGen. Twelve healthy males were administered GlucaGen 1 mg IM. Plasma samples were collected up to 4 hours post-dose and pharmacokinetic parameters are summarized in Table 1.

APPEARS THIS WAY ON ORIGINAL

Table 1. GlucaGen Pharmacokinetic Parameters

PK Parameter	Data	Mean	SD	Median	Min	Max
$AUC_{0-4\ hrs}$ (pg*min/mL)	Raw	112670.8	43620.0	109150.0	(b)(4)	
	*Corrected	*93992.4*	*43682.0*	*87141.3*		
C_{max} (pg/mL)	Raw	1685.7	732.5	1650.5		
	*Corrected	*1627.5*	*730.4*	*1604.2*		
T_{max} (min.)	Raw	17.9	23.4	12.5		
	*Corrected	*17.9*	*23.4*	*12.5*		

* Corrected = Average of 3 baseline readings subtracted from all samples.

One subject had a Tmax of 90 minutes; this remains unexplained. All other subjects had Tmax values between 5 and 20 minutes.

It is important to note that the mean Cmax value in study 007 was lower than the mean Cmax values from IM glucagon studies conducted by Novo Nordisk in 1988. In those earlier studies, mean Cmax values (b)(4) According to John Strong (personal conversation), results from RIAs can change over time, for example, as specificity of antibodies increases. The sponsor was asked to address the discrepant results between old and new studies and they submitted a publication, 'Report of the American Diabetes Association's Task Force on Standardization of the Insulin Assay' David C. Robbins, et al. Diabetes 45:242-256, 1996, which compiled information across many laboratories. Although this article addressed (b)(4) comments regarding differences reported across laboratories are relevant:

> ...the differences could be caused by differing behaviors (specificity of the anti-insulin antibodies and the poorly understood complex nature of the biological reaction central to immunoassays) of the polyclonal and monoclonal antibodies used in each assay.

Thus, the discordant Cmax values generated in study 007 may be an artifact of the time between assays, and were as 'true' as previous assay results.

Subject 10 from study 007 was the only subject reported with an adverse effect. This subject reported moderately severe symptomatic hypoglycemia. However, no blood glucose information could be located

in the report. Upon further investigation of the pre-study labs, it was learned that this subject had a serum potassium reported at 1.5 mmol/L [redacted]; the value of 1.5 mmol/L is almost incompatible with life. All demographics and glucagon pharmacokinetic parameters for this subject were similar to other subjects.

[redacted]

COMMENTS TO BE SENT TO SPONSOR

1) Subject 10 was reported to have a pre-study serum potassium of 1.5 mmol/L, a value almost incompatible with life. The sponsor should clarify how a healthy subject with such a potassium was enrolled in the study. — This comment was conveyed to Novo during 6/10 t-con + their response is filed under the "FDA Letters + Memos" Tab.

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)

1) CLINICAL PHARMACOLOGY

[redacted]

[redacted] IM injection of GlucaGen resulted in a mean (CV%) Cmax of 1686 pg/mL (43%) and median Tmax of 12.5 minutes. The mean apparent half-life of 45 minutes after IM injection probably reflects prolonged absorption from the injection site. Glucagon is degraded in the liver, kidney and plasma. — Faxed to the sponsor on 6/10/98

☛ Cmax, Tmax, and half-life values were from study 007. (half-life calculated as Ln(2)/-k where k is slope of Ln(conc.) vs time)

/s/ [redacted] 10-JUN-98

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

[redacted]

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 6/10/98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /s/ [redacted] 6/10/98

CC: NDA 20-918/N-000 (orig.,1 copy), HFD-510(Misbin, RheeJ), HFD-340 (Viswanathan), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: AE [redacted]

Appendix 1. Study summaries

TITLE OF TRIAL Pharmacokinetic Assessment of Glucagon after Intramuscular Injection	
INVESTIGATOR (b)(4) [redacted]	
TRIAL CENTER (b)(4) [redacted]	
PUBLICATIONS None.	
TRIAL PERIOD 30 April 1998 to 7 May 1998	**DEVELOPMENT PHASE** Phase I
OBJECTIVES To provide C_{max} and $AUC_{0-4\ hrs}$ values for GlucaGen® using an assay validated for the entire range of concentrations in samples obtained after single intramuscular dose in healthy subjects.	
METHODOLOGY An open, single-dose study.	
NUMBER OF SUBJECTS 12:Planned, 27:Screened, 7:Screen Failed, 20:Dosed, 12:PK Analysis, 20:Safety Evaluation.	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION Healthy males (b)(4) [redacted] body mass index (b)(4) [redacted] fasting blood glucose (≤ 108 mg/dl) ≤ 6 mmol/l.	
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER GlucaGen 1 mg Vial, Batch No. HR40162, Exp. 25 Feb 1999 with Sterile Water for Reconstitution 1 mL, Batch No. GR41031, Exp. 14 Aug 2000..	
DURATION OF TREATMENT One day.	
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER None.	
CRITERIA FOR EVALUATION - PHARMACOKINETIC PARAMETERS Pharmacokinetic variables evaluated for glucagon were $AUC_{0-4\ hrs}$, C_{max} and T_{max}. **CRITERIA FOR EVALUATION - SAFETY** The primary evaluation of safety was spontaneous adverse events. Vital signs, height, body weight, physical examination, laboratory and electrocardiographic data were collected and evaluated as screening parameters.	

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STATISTICAL METHODS

Pharmacokinetic parameters ($AUC_{0-4\ hrs}$, C_{max} and T_{max}) were calculated for 12 subjects. A listing of adverse events, vital signs, height and weight, and laboratory screening assays (chemistry, hematology, and urinalysis) were provided for 20 dosed subjects.

PHARMACOKINETIC RESULTS

The final overall pharmacokinetic parameters of glucagon measured in 12 healthy male subjects were as follows:

PK Parameter	Data	Mean	SD	Median	Min	Max
$AUC_{0-4\ hrs}$	Raw	112670.8	43620.0	109150.0	64437.5	204050
(pg*min/mL)	*Corrected	*93992.4*	*43682.0*	*87141.3*	*48935.0*	*186567*
C_{max} (pg/mL)	Raw	1685.7	732.5	1650.5	712.0	2930.0
	*Corrected	*1627.5*	*730.4*	*1604.2*	*667.0*	*2883.7*
T_{max} (min.)	Raw	17.9	23.4	12.5	5.0	90.0
	*Corrected	*17.9*	*23.4*	*12.5*	*5.0*	*90.0*

* *Corrected = Average of 3 baseline readings subtracted from all samples.*

SAFETY RESULTS

Administration of a single IM dose of glucagon in 20 healthy male subjects was safe. One subject (No. 10) reported moderately severe symptomatic hypoglycemia. This was an isolated event considered by the investigator to be probably related to glucagon dosing. The subject was monitored and recovered fully before discharge from the study site that same day. There were no other reports of adverse events.

CONCLUSIONS

Pharmacokinetic parameters ($AUC_{0-4\ hrs}$, C_{max} and T_{max}) for a 1 mg glucagon (GlucaGen®) injection were determined in 12 healthy male subjects. None of the determined glucagon concentrations were above the validated upper range of the assay (44 - 10000 pg/mL.) The administration of glucagon was also found to be safe in all 20 dosed subjects.

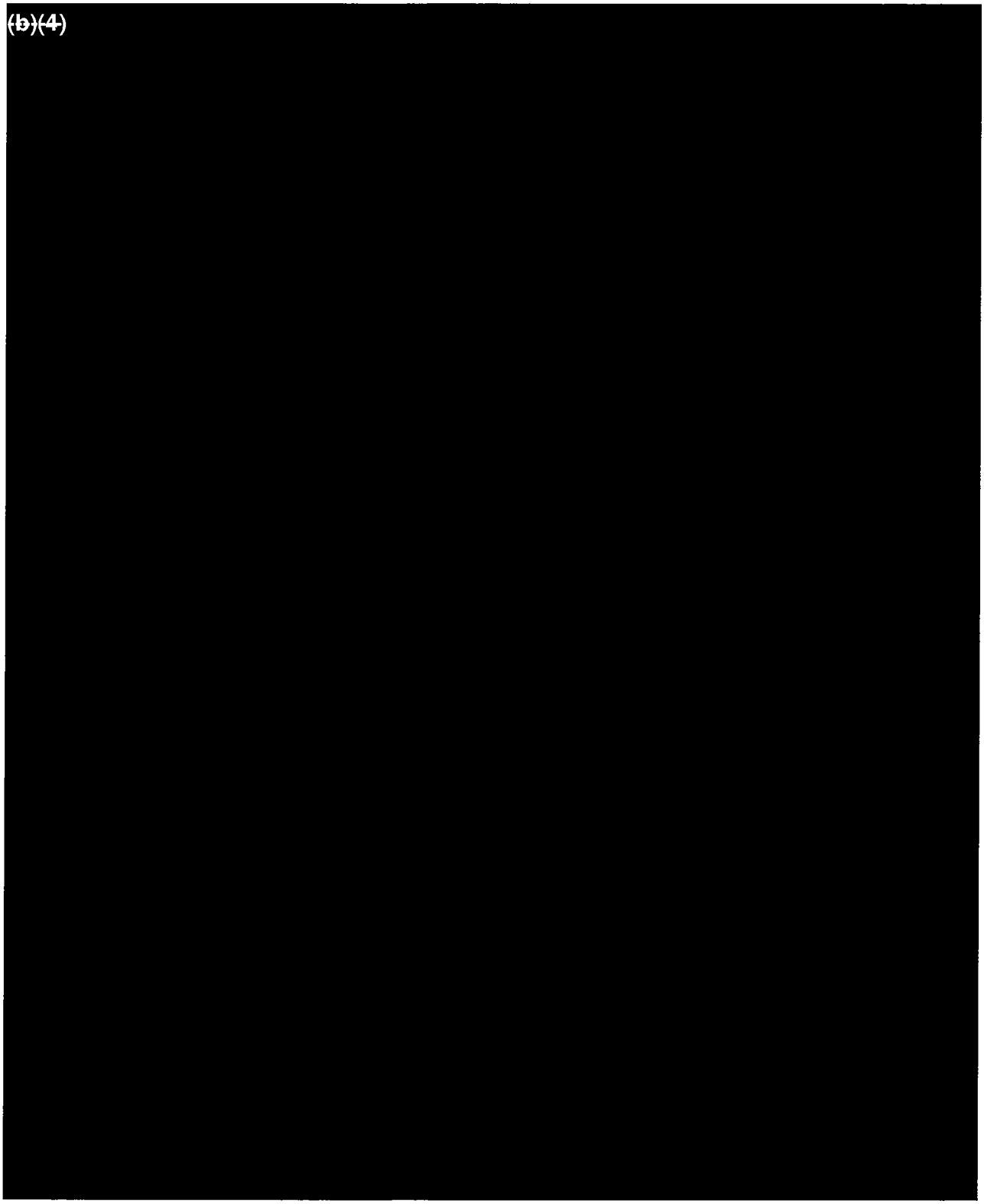
Ethics Committee and written informed consent were obtained prior to starting the trial. The trial was conducted in accordance with the Helsinki Declaration and with Good Clinical Practice.

[redacted]

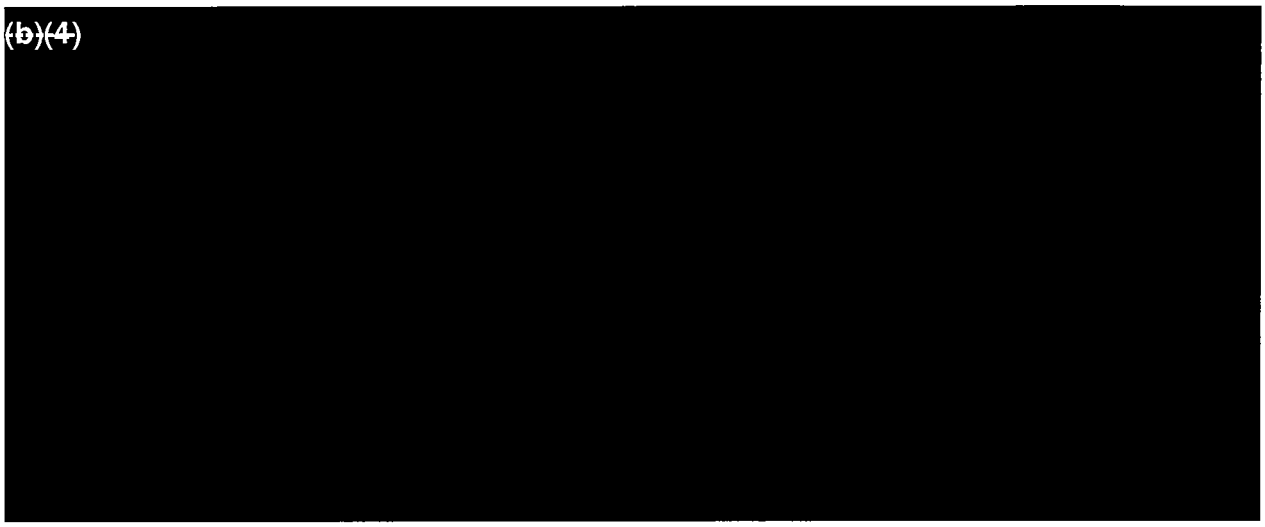
Appendix 2. Assay performance

COMMENTS: John M. Strong, Ph.D., CDER/OPS/OTR/LCP 6/4/98

(b)(4)



(b)(4)



APPEARS THIS WAY ON ORIGINAL

JUN 3 1998

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-918	**SUBMISSION DATE:** **22-MAY-98**
BRAND NAME:	**GlucaGen ® 1mg**
GENERIC NAME:	**rDNA glucagon**
REVIEWER:	**Robert M. Shore, Pharm.D.**
SPONSOR:	**Novo Nordisk Pharmaceuticals, Inc., Princeton, NJ**
TYPE OF SUBMISSION:	**BL: Labeling**

SUBMISSION: [redacted]

This submission contains important but minor labeling changes for the 'Description' and 'How Supplied' sections of the labeling as well as for 'Information for the Patient'. These changes are acceptable to OCPB.

/s/ [redacted]
Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics
03-JUN-98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader (b)(4) [redacted] 6/3/98

CC: NDA 20-918/N-000 (orig.,1 copy), HFD-510(RheeJ, Misbin), HFD-870(Shore, Ahn, M. Chen), CDR (Barbara Murphy).

Code: AE

[redacted]

Comments faxed to the sponsor on 5/28/98

ORIGINAL MAY 19 1998

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-918/N-000	**SUBMISSION DATE:**	**06-May-98**
BRAND NAME:	**GlucaGen®**	
GENERIC NAME:	**glucagon (rDNA) 1mg for injection**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Novo Nordisk Pharmaceuticals, Inc., Princeton, NJ**	
TYPE OF SUBMISSION:	**BB: Assay validation data**	

SYNOPSIS:

This submission consisted of initial results from the (b)(4) for glucagon for protocol 007, 'Pharmacokinetic Assessment of Glucagon after Intramuscular Injection'. Also included in the submission was an 'Assay Summary' (b)(4) Previously, two assays were determined to have been unacceptable, so the sponsor was requested to submit assay validation data before completing the current study.

REVIEW:

(b)(4)

(b)(4)

[redacted]

/s/ [redacted] 19-MAY-98

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/s/ [redacted]

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

/s/ [redacted] 5/19/98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

CC: NDA 20-918/N-000 (orig.,1 copy), HFD-510(RheeJ, Misbin, Fleming), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: NA

APPEARS THIS WAY ON ORIGINAL

[redacted]

APPENDIX 1. Assay Summary

REDACTED __2__ PAGES OF TRADE SECRET AND/OR CONFIDENTIAL COMMERCIAL INFORMATION

JUN - 8 1998 J. Rhee

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-918/N-000	**SUBMISSION DATE (TYPE):**	**05-MAY-98**
BRAND NAME:	**GlucaGen® 1 mg**	
GENERIC NAME:	**glucagon (rDNA) for injection**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Novo Nordisk Pharmaceuticals, Inc. Princeton, NJ**	
TYPE OF SUBMISSION:	**C: Assay report**	

SYNOPSIS:

The submission is a hard copy of a FAX that was previously reviewed (See submissions on 12-MAR-98 and 16-MAR-98). It was determined, in that review, that the (b)(4) to which this report refers was not reliable.

/s/ [redacted] 08-JUN-98

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 20-918/N-000 (orig.,1 copy), HFD-510(RheeJ), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: NA

APPEARS THIS WAY ON ORIGINAL

Comments faxed 5-21-98 Rhee

MAY 13 1998

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-918/N-000	**SUBMISSION DATE (TYPE):**	**12-MAR-98 (AB)** **16-MAR-98 (BB)**
BRAND NAME:	**GlucaGen® 1 mg**	
GENERIC NAME:	**glucagon (rDNA) for injection**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Novo Nordisk Pharmaceuticals, Inc. Princeton, NJ**	
TYPE OF SUBMISSION:	**AB: Study Report (b)(4)**	

SYNOPSIS:

The submission on 12-MAR-98 was a final study report from Study 101 entitled "A comparison of the relative bioavailability of glucagon Novo (ge) and glucagon Novo given intramuscularly to healthy volunteers"; 'ge' denotes genetically engineered (rDNA). This report was submitted to fulfill the requirement in 21CRF 320.21 which indicates that the NDA shall include evidence demonstrating the *in vivo* bioavailability of the drug product (the original NDA submission 18-SEP-97 contained an assay that was deemed 'unreliable').

The submission on 16-MAR-98 was (b)(4) for Study 101. In addition, there was 1) a FAX sent on 29-APR-98 which consisted of a validation report (b)(4) and 2) a teleconference on 29-APR-98 with members of Novo Nordisk (b)(4) where the assay was conducted in 1988.

After reviewing these data, OCPB has deemed this assay unacceptable because there was a lack of validation data in the range where many of the samples (especially Cmax samples) were assayed. As such, no determination could be made about the reliability of the reported data and, therefore, the study report was not reviewed.

ASSAY REVIEW:

APPEARS THIS WAY ON ORIGINAL

Study 101 was a cross-over design in which 12 healthy male subjects received Novo glucagon (pancreatic extract) and Novo glucagon (b)(4) rDNA). The objective was to compare the bioavailability of the two products administered in 1 mg IM doses. This study was conducted in 1988. The plasma samples obtained from this study were assayed for glucagon (b)(4) using a

(b)(4)

1. Accuracy/Recovery: The only accuracy data submitted were those that were provided in the **kit insert**; (b)(4) did not submit any accuracy data that were generated in **their** lab. The kit insert suggested the following recovery:

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Conc. (pg/mL)	Mean % Recovery (N=4)
25	104.7
50	98.3
125	95.8
250	99.5
500	100.8
1000	109.0

However, this was no indication of the recovery of the assay when performed in the (b)(4) factors like pipetting technique and personnel could effect the performance of an assay.

2. Precision: Double determinations for the concentration of glucagon were made for each sample from subjects in the study. Intra-assay variability (repeatability) was determined by calculating the (b)(4) each sample (12 subjects in 2-way crossover with 17 samples per subject per treatment; Nmax=408 sample points). The validation report noted that the 'limitation of this evaluation is that only 2 data points are available for each (b)(4) was ≤ 14% for all sample points.

For intermediate precision (inter-assay variability), a low (mean determined value 118 pg/mL) and high (mean determined value 502 pg/mL) QC were used. The CV for the low and high QC (N=13 determinations) were 14% and 6%. There were no QCs above 502 pg/mL. (Note: about 82/187 (45%) of the Novo (ge) data points were above 600 pg/mL)

In addition, there were other QCs as follow:

Mean Determined Conc. (pg/mL)	CV% (N=13 determinations)
213	8.7
256	8.9
103	21.6

These QCs were all below 300 pg/mL. Therefore, there was no indication of the precision of the assay above about 500 pg/mL when (b)(4)

3. Linearity: The sponsor evaluated 1:4 dilution of the high control (about 500 pg/mL) since many samples around Cmax underwent this 1:4 dilution. The results (b)(4) demonstrated that the ratio of undiluted to diluted high control had a mean of 0.97 and CV of 10%. The kit insert had data on this 1:4 dilution as follows:

Sample	Baseline (pg/mL)	1:4 Dilution	Ratio (undiluted/diluted)
#1	900	280x4=1120	0.80
#2	440	125x4=500	0.88

These data indicated that, for the 1:4 dilution, (b)(4) performed better than the kit predicted. There were (b)(4) from one subject (Subject 3) which underwent a 1:8 dilution; however, the reliability of such a dilution has not been determined.

4. Range: The kit contained standards at the following concentrations: 0, 25, 50, 100, 250, 500, 1000, and 2000 pg/mL. However, the validation data, as generated (b)(4) covered only the lower end of this range (i.e., ≤ about 500 pg/mL). Therefore, assayed concentrations above about 500 pg/mL were of questionable reliability.

5. Specificity: The kit insert provides adequate specificity parameters.

CONCLUSION:

Of major concern was the lack of precision and accuracy data above 500 pg/mL. About 45% of the (b)(4) (b)(4) data were above 600 pg/mL, a range for which there was little, if any, information on the performance of the assay. The only QCs run by the lab were between 100 and 500 pg/mL; there was no specific QC information above 500 pg/mL from the actual lab conducting the kit assay.

In addition, Cmax was reported to be > 1000 pg/mL (diluted) in 6 out of 11 subjects receiving (b)(4) Even the kit insert had no data in the (b)(4), although the kit included a 2000 pg/mL standard. So, basically, any information about Cmax in more than half of the subjects was of questionable validity.

The 1992 conference report ("Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies" Shah-VP; Midha-KK; Dighe-S; McGilveray-IJ; Spector-S; et-al. Pharm Res; 1992; 9; 588-592.) suggested certain elements of a validated assay. These included the determination of accuracy and precision using replicate sets of at least 3 QCs representing the low end, center, and upper end of the standard curve. For this glucagon (b)(4) there was no validation data for the upper end of the standard curve.

Given the uncertainty of the assay results, OCPB could not accept the assay as valid and, therefore, did not review the study report.

APPEARS THIS WAY ON ORIGINAL

COMMENTS TO BE SENT TO SPONSOR

1) On 30-APR-98 a teleconference between Novo Nordisk (Mary Ann McElligott) and FDA (Robert Shore, Julie Rhee) was conducted. Novo was informed that the assay validation that was submitted on 16-MAR-98 and FAXed on 29-APR-98 were not acceptable and that the planned study to begin the following Monday should proceed. Also, as per a suggestion made by Dr. Misbin (FDA Medical Officer), the sponsor should submit information as soon as possible on assay validation for this new study.

2) It is suggested that the sponsor refer to the following report for suggestions on assay validation criteria: 'Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies' Shah-VP; Midha-KK; Dighe-S; McGilveray-IJ; Spector-S; et-al. Pharm Res; 1992; 9; 588-592. Also available in Int-J-Pharm (International-Journal-of-Pharmaceutics); 1992; 82(Apr 20); 1-7. Also of general use is the ICH document Q2A, 'Guideline for Industry: Text on Validation of Analytical Procedures.'

/s/ [redacted] 13-MAR-98

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 11-MAY-98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /s/ [redacted] 5/13/98

CC: NDA 20-918/N-000 (orig.,1 copy), HFD-510(RheeJ, Misbin, Fleming), HFD-870(Shore, Ahn, ChenME), CDR (Barbara Murphy).

Code: NA

[redacted]
APPEARS THIS WAY ON ORIGINAL

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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-918/N-000	**SUBMISSION DATES:**	**09/18/97** **10/29/97(BB)** **11/06/97(BB)** **12/16/97(BM)** **01/15/98 (BL)**
BRAND NAME:	**GlucaGen™**	
GENERIC NAME:	**glucagon (rDNA) 1 mg (1 IU) for injection**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Novo Nordisk Pharmaceuticals, Inc., Princeton, NJ**	
TYPE OF SUBMISSION:	**505 (b) (2); Code: 3P**	

FEB 20 1998

TERMS AND ABBREVIATIONS:

AUCa-b ..... area under the plasma-concentration-time curve from time a to time b
DMEDP ..... Division of Metabolic and Endocrine Drug Products
IM ..... intramuscular
IU ..... international unit
N/A ..... not available
OCPB .. .. Office of Clinical Pharmacology and Biopharmaceutics
rDNA ... . recombinant DNA
RIA ..... radioimmunoassay
SC ..... subcutaneous

APPEARS THIS WAY ON ORIGINAL

SYNOPSIS:

The sponsor is seeking approval of GlucaGen™, (4)(4) for use in 1) treating hypoglycemia and 2) diagnostic gastrointestinal procedures. The NDA includes a phase I bioequivalence study comparing GlucaGen™ vs. approved animal-source glucagon (Glucagon, Eli Lilly) injected IM. However, the (4)(4) was improperly used and, therefore, the pharmacokinetic results are invalid. The pharmacodynamic measurement of plasma glucose is acceptable and comparison of AUC and Cmax of the two products met the (0.8-1.25) confidence interval criteria.

APPEARS THIS WAY ON ORIGINAL

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 20-918/N-000 submitted 09/18/97, 10/29/97, 11/06/97, 12/16/97, and 01/15/98. The overall Human Pharmacokinetic Section is not acceptable to OCPB because the concentrations of plasma glucagon in samples were generally (b)(4) used. Since pharmacokinetic data is the primary basis for any bioequivalence determination (b)(4)

The only useful data generated in the bioequivalence study was the pharmacodynamic endpoint of plasma glucose. Analysis of this data demonstrates that the ratio of AUC and Cmax for the two glucagon products falls (b)(4) OCPB accepts this as a demonstration of therapeutic equivalence. DMEDP should also decide if therapeutic equivalence has been demonstrated to their satisfaction. This recommendation and labeling comments (p. 6) should be sent to the sponsor as appropriate.

APPEARS THIS WAY ON ORIGINAL

Table of Contents

(b)(4)

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BACKGROUND:

Glucagon is a single chain polypeptide hormone responsible for the stimulation of glucose output from hepatic glycogen depots. The chemical structure of glucagon is preserved across human, porcine and bovine species. Currently the only product available on the U.S. market is animal source glucagon produced by Eli Lilly. According to the NDA (Volume 1, page 55), over 40 other countries have approved GlucaGen® for marketing.

The sponsor is seeking approval (b)(4) This is a 505(b)(2) application that has received priority review status from the Agency.

Volumes 1.1, 1.13, and 1.14 were reviewed by OCPB.

PROTOCOL INDEX

Protocol Number	Title	Page
GLU/DCD/006/USA	Bioequivalence of (b)(4) glucagon (GlucaGen®) and glucagon purified from bovine and pig pancreas injected intramuscularly: a randomized, open-labeled, 2-period cross over single-center study	p. 17

DRUG FORMULATION: APPEARS THIS WAY ON ORIGINAL

GlucaGen® contains the following ingredients:

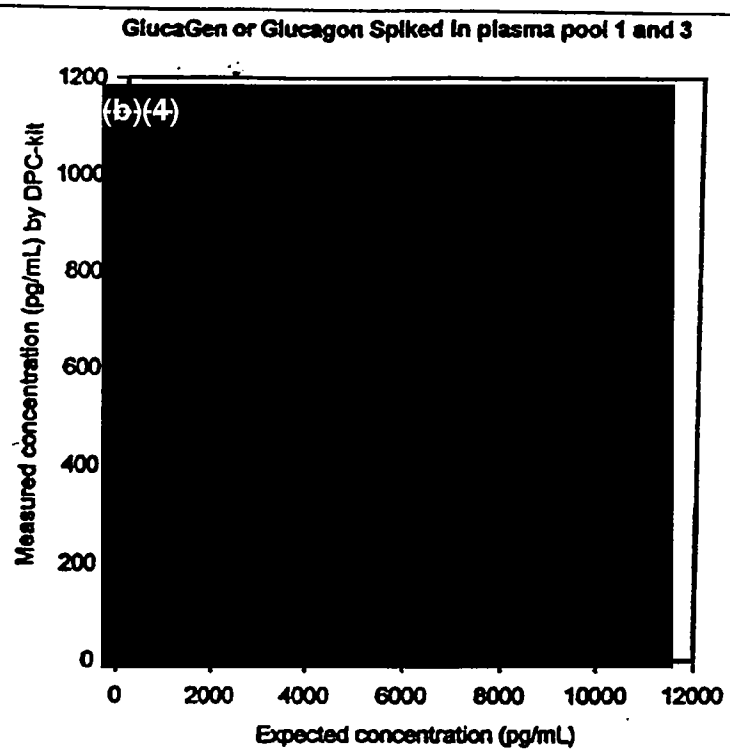
Substance	Amount
glucagon HCl	(b)(4)
Lactose Monohydrate	107 mg

A vial of sterile water for reconstitution (b)(4) is also provided. Batch 67679, used in the bioequivalence study, was of commercial size and was manufactured under commercial conditions.

ANALYTICAL METHODOLOGY:

The (b)(4) was deemed "not reliable" by John Strong, Office of Testing and Research (see Appendix 3). The major problem with the (b)(4) (b)(4) [redacted] However, applying the correction results in assay error that is unacceptable.

APPEARS THIS WAY ON ORIGINAL



Plot of results: ▲, Glugagon (Lot 611002) spiked in plasma pool 1; ⊙, Glucagon (Lot 611002) spiked in plasma pool 3; ▼, GlucaGen (Lot 67679) spiked in plasma pool 1; □, GlucaGen (Lot 67679) spiked in plasma pool 3; –, The fitted curve.

Figure 1

(b)(4)

APPEARS THIS WAY ON ORIGINAL

(b)(4)

[redacted]

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioequivalence

(b)(4)

[redacted]

In the bioequivalence study GLU/DCD/006/USA, 36 healthy subjects received 1 mg IM doses of (b)(4) [redacted] glucagon (reference) and GlucaGen® (test) on two separate occasions. Blood for glucose analysis was collected pre-dose and over 180 minutes post-dose. AUC0-180 for each subject was calculated using the linear trapezoidal rule while observed Cmax and Tmax values were used for analysis. Parameters were ln-transformed for comparisons. The 90% CI for the mean ratio of AUC0-180 and Cmax are ((b)(4) [redacted] (b)(4) [redacted]). Tmax for plasma glucose was 29 minutes with GlucaGen® and 32 minutes with glucagon. Since the ratios of AUC and Cmax for these two products falls within the (0.8-1.25) interval, OCPB accepts these products as therapeutically equivalent.

(b)(4)

[redacted]

APPEARS THIS WAY ON ORIGINAL

LABELING COMMENTS:

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

1) CLINICAL PHARMACOLOGY

Glucagon is rapidly absorbed from sc or im injection with maximal glucagon concentration achieved within (b) 15 minutes.

☛ Two references are given for this statement. One is the USPDI: this reference gives no indication of Tmax for glucagon. The second reference is Volume 12, pages 12-17. Here, the results from a number of studies are summarized and, from the data presented, Tmax is about 8 minutes or 13-15 minutes after either an SC or IM dose, respectively.

/s/ [redacted] 02/20/98

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 02/19/98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /s/ [redacted] 2/20/98

CC: NDA 20-918/N-000(orig.,1 copy), HFD-510(RheeJ, Misbin, Berlin, RheeH), HFD-340(Viswanathan), HFD-870(Shore, Ahn, ChenME), CDR(MurphyB).

Code: NA

~~APPEARS THIS WAY ON ORIGINAL~~ [redacted]

Memorandum

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

APPEARS THIS WAY ON ORIGINAL

Date: 02/23/98
From: Robert M. Shore, Pharm.D.
To: Hae-Young Ahn, Ph.D.
Re: Addendum to GlucaGen7 (rDNA glucagon) review dated 02/20/98
NDA 20-918/N-000
Novo Nordisk Pharmaceutical, Inc.

APPEARS THIS WAY ON ORIGINAL

Synopsis:

On 02/20/98 The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) had completed a review for NDA 20-918/N-000 dated 09/18/97, 10/29/97, 11/06/97, 12/16/97, 01/15/98. Based on this review, DPE-2 had determined that the application is **not approvable** because (b)(4) This addendum further explains what the sponsor should do in response to this non approval.

As CRF 320.21 indicates, the NDA shall include evidence demonstrating the *in vivo* bioavailability of the drug product. In addition, CFR 320.25 (e) indicates that the purpose of an in vivo study is to determine the relative bioavailability as compared to an appropriate reference material. Since the assay in the original NDA submission was not acceptable, the pharmacokinetic profile and bioavailability of GlucaGen have not been established.

Comments to be sent to sponsor:

(b)(4)

sponsor. A similar design as GLU/DCD/006/USA would be acceptable, but the sponsor should submit the protocol for such a study well in advance of initiating the study.

CC: NDA 20-918/N-000 (orig., 1 copy), HFD-510(Misbin, RheeJ, Berlin), HFD-870(Ahn, Shore, ChenME), CDR (Barbara Murphy)

J. RHEE

NOV 1 1 1997

Memorandum

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:	11/14/97
From:	Robert M. Shore, Pharm.D. /s/ 11/14/97
To:	Hae-Young Ahn, Ph.D., Team Leader
Re:	Filing for NDA 20,918/N-000
	GlucaGen®
	Novo Nordisk

The sponsor has submitted assay validation data in response to our letter dated 10/22/97. Data submitted (b)(4) has been reviewed by The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2. Based on this review, the Division has determined that the application is fileable

CC: NDA 20,918/N-000 (orig., 1 copy), HFD-510(Misbin, J.Rhee), HFD-870(Ahn, Shore, M. Chen)

APPEARS THIS WAY ON ORIGINAL