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APPLICATION NUMBER: 020918

MEDICAL REVIEW(S)

FEB -2 1998

New Drug Application

NDA 20-918

GlucaGen (Glucagon (rDNA))

Submitted by Novo Nordisk letter date: 18 September 1997

stamp date: 24 September 1997

documents reviewed: volumes 1.1, 1.12, 1.14

amendments submitted October 15, 1997

December 16, 1997

Safety update submitted January 20, 1998

Adverse event report to IND 47,342

Submitted December 23, 1997

MEDICAL OFFICER'S REVIEW

January 31, 1998

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GlucaGen = Glucagon (rDNA) from Novo-Nordisk

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Introduction

GlucaGen is recombinant glucagon from yeast which has been available in Europe since 1992. The product was marketed in Australia in 1994 and in Japan in May 1996. Total world-wide distribution has been about (b)(4) distributed through June 1996 alone.

(b)(4)

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The drug substance in this product has the same amino acid sequence as the animal-sourced pancreatic glucagon that is currently available in the United States. Its major indications are treatment of hypoglycemia, particularly for self-administration by diabetic patients taking insulin, and to relax contractions during diagnostic gastrointestinal procedures. Intravenous glucagon is also used as a diagnostic test to distinguish type 1 from type 2 diabetes on the basis of C peptide secretion. Since GlucaGen's chemical structure and indications are identical with animal-sourced glucagon currently marketed by Eli Lilly, the basis for approval of this NDA could potentially rely on the bioequivalence data which the Sponsor has submitted (006/USA). In addition, the submission contains clinical studies documenting efficacy and safety which formed the basis of approval in Europe.

The section, entitled "Previous studies outside the United States" includes data from 18 clinical trials with total exposure of 438 patients and 164 normal volunteers.

**Number of Subjects Exposed to Glucagon
in 18 Clinical Trials**

Product	Normal	Patients	Total
GlucaGen			
Total	164	438	602
<i>im</i>	84	311	395
<i>iv</i>	18	127	145
<i>sc</i>	62	0	62
Pancreatic			
Total	56	177	233
<i>im</i>	34	146	180
<i>iv</i>	0	31	31
<i>sc</i>	22	0	22

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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. Lilly has also informed us that their extraction facilities are old and they would eventually like to switch production entirely to recombinant glucagon themselves. The availability of Lilly's animal-sourced glucagon has also been threatened by quality assurance problems. In October 1995, DMEDP was informed that a lot of glucagon failed to pass safety screening. Indeed, intravenous injection of this glucagon into mice resulted rapidly in death in all animals tested. The cause of this problem was gelling of the glucagon solution after reconstitution. Although, the problem has been solved by lowering the pH of the diluent, this episode illustrates the perils of having only one glucagon supplier. Finally, as Lilly has also acknowledged, fear of bovine spongiform encephalopathy has cast a cloud of uncertainty over all beef products worldwide. Although we believe a fear of BSE from Lilly glucagon to have little rational basis, the issue could easily be made moot by the introduction of rGlucagon into the United States. For these reasons, I have asked that this NDA be given a priority review.

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Previous Studies Outside the United States:

Pharmacokinetics/Pharmacodynamics

Study 1 (101 UK) was a double blind cross-over study of 1 mg intramuscular injection of Glucagon (rDNA) vs pancreatic glucagon in 12 healthy male volunteers. The study report was dated June 1988. Treatments were 1 week apart. In addition to PK variables, glucose, insulin and C peptide were measured as PD variables. The results, shown in the table and figure, indicate that glucagon (rDNA) is essentially equivalent to pancreatic glucagon. Somewhat greater effect on insulin and C peptide with glucagon (rDNA) can be accounted for by the slightly higher blood levels. This protocol is essentially the same as one done in Japan (study 2). Again, the two preparations were found not to be statistically different. In comparison to the UK study, C max was slightly higher in Japan (5029 vs 4481 pg/ml) and T max was somewhat briefer (9.2 min vs 15 min).

Study 101/UK

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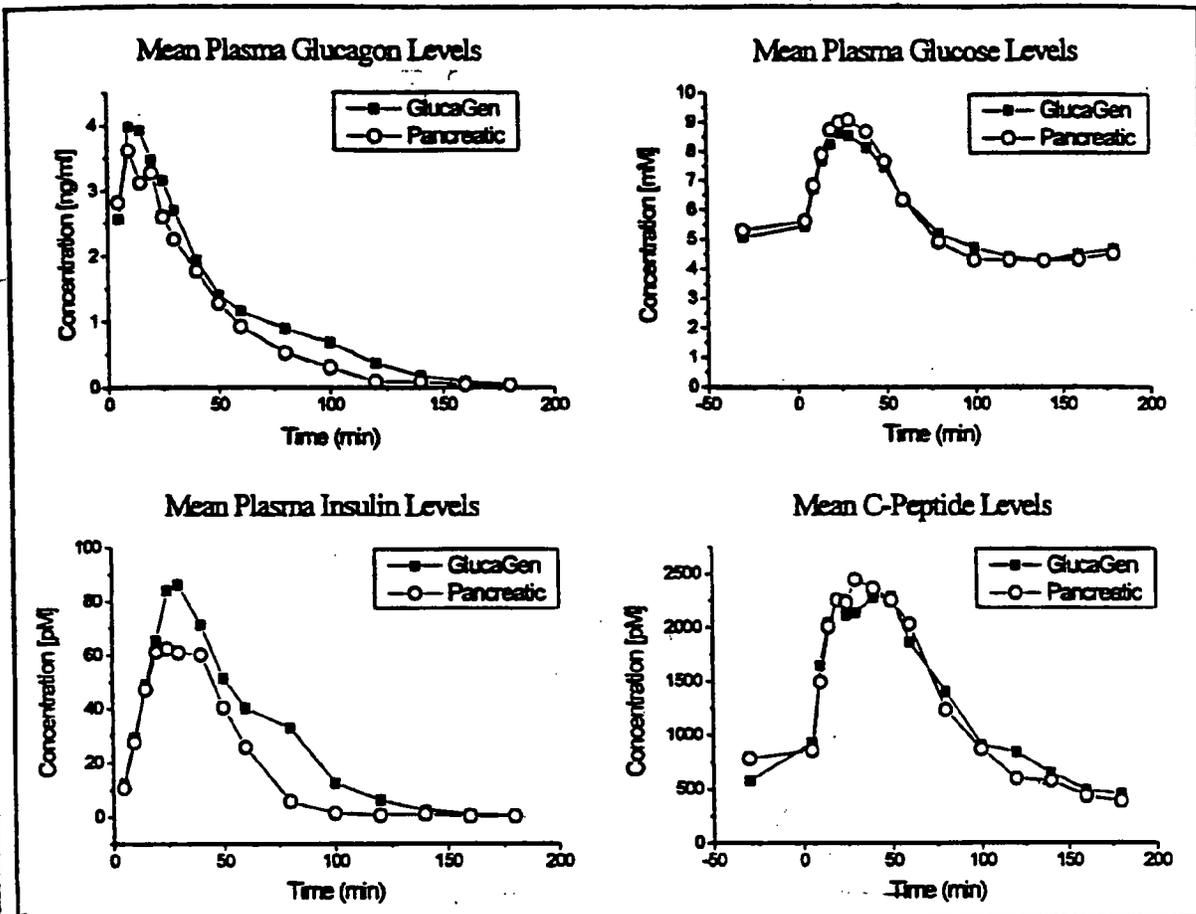
Serum Glucagon

	Glucagon (rDNA)	Pancreatic Glucagon	P-Value
C _{max} (pg/ml) mean (SD)	4481 (2153)	4118 (1310)	0.6356
T _{max} (h) mean (range)	0.25 (15)(44)	0.21 (15)(44)	0.8585
AUC _T (pg/ml*hr) mean (SD)	3338 (2125)	2649 (924)	0.3512
AUC _I (pg/ml*hr) mean (SD)	3377 (2156)	2673 (935)	0.3483
K _d (1/h), mean (SD)	2.14 (0.87)	2.18 (0.85)	0.9235
T _{1/2} (hr), mean (SD)	0.38 (0.16)	0.36 (0.12)	0.6661
p-value from comparison			

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BEST-POSSIBLE

Glucagon (rDNA)



After Glucagon (GlucaGen) injection, plasma glucagon C_{max} , AUC_7 , and AUC_1 were consistently equal to or greater than pancreatic glucagon. Differences in Pk parameters, including T_{max} , K_{el} , and $T_{1/2}$ for the two glucagon preparations were not statistically significant.

There were no significant differences in C_{max} , T_{max} , and AUC for glucose or insulin between the two groups. The only statistically significant differences were in C-peptide levels, at 50, 120, 140, 160, and 180 minutes. Values were higher for recombinant glucagon than pancreatic glucagon. Confidence intervals did not indicate bioequivalence, perhaps in part because of the small number of subjects ($n=12$) in the study. These differences were not considered clinically relevant.

BEST-POSSIBLE

Study 3 (001 USA) was a cross-over comparison of glucagon(rDNA) with pancreatic glucagon marketed by Eli Lilly in 18 normal male subjects. There was a minimal 6 day wash-out between dosing. Plasma glucagon, glucose, insulin and C-peptide were measured. I patient was deleted from analysis because he was found to have exceptionally high plasma glucagon levels after injection of pancreatic glucagon. Results did not show any statistically significant differences between the two preparations; however, the C max of 1462 pg/ml was considerably less than C max obtained in other studies. It was noted that the glucagon batch was not produced by GMP standards and did not meet all stability specifications.

Study 4 (016/Japan) compared 1 mg GlucaGen given iv vs subcutaneously. As shown in the table, T max for iv glucagon with respect to glucose was shorter than for subcutaneous glucagon (20.6 vs 33 minutes) but the glucose levels were higher with subcutaneous glucagon.

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Study 016/Japan

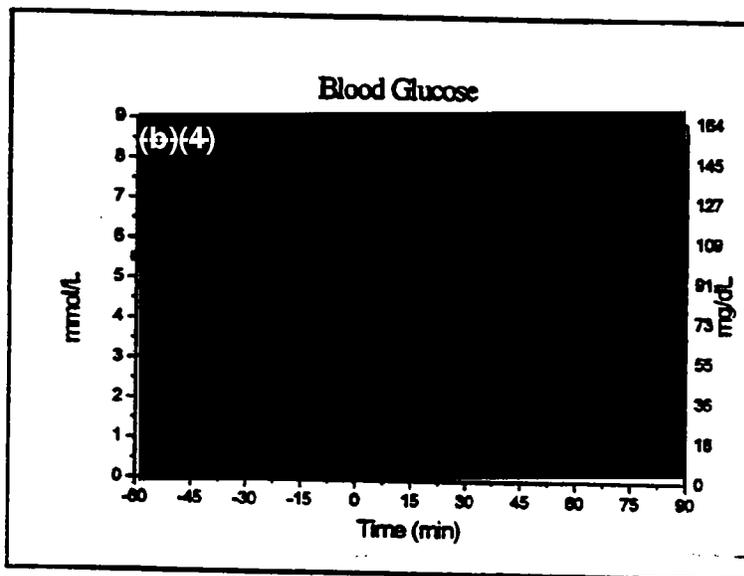
	Glucagon mean \pm SD		Glucose mean \pm SD	
	sc	iv	sc	iv
T _{max} (min)	8.0 (3.7)	-	33.0 (3.7)	20.6 (1.8)
C _{max} (pg/ml) (glucose = mg/dl)	6629 (476)	-	160.4 (8.4)	123.4 (2.7)
AUC (pg*hr/ml)	4710 (310)	6394 (937)	215.4 (13.6)	174.4 (4.5)
T _{1/2} (min)	19.9 (1.5)	3.1 (0.2)	-	-

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Treatment of Severe Hypoglycemia

Study 5 (095 /Denmark) consisted of 12 male patients with type 1 diabetes who received insulin to bring their blood glucose to about 36 mg/dl. They then received 1 mg of Glucagon(rDNA). As shown in the figure, blood glucose returned to above 55 mg/dl by 15 minutes and to pre-infusion levels by 30 minutes after injection. Peak glucagon concentration was achieved at about 15 minutes and was reported to be about 3 ug/l in Diab Res Clin Prac 17, 1992, (b)(4)

Study 095/Denmark



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Study 6 (028/Japan) was conducted in patients with type 1 and type 2 diabetes which compared glucose raising effect of im vs iv glucagon. 20 minutes after a 1 mg dose, patients who received glucagon iv went from a mean glucose of (b)(4)

(b)(4) Patients who received glucagon IM went from (b)(4)
(b)(4)

Study 028/Japan

Blood Glucose (mg/dl)

<u>Number of Patients</u>	<u>Start</u>	<u>20 minutes</u>
Glucagon (DNA) iv, 21	76.4	125.7
Glucagon (DNA) im, 17	58.1	113.2

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Study 7 (090/Denmark) was a comparative study of recombinant vs pancreatic glucagon given intravenously to treat insulin-induced hypoglycemia in 10 healthy males. Subject received infusions of somatostatin, phentolamine and propranolol to block endogenous hormone release. Baseline glucose of 5 mM fell to less than 2 mM by 30 minutes after insulin. Glucose values returned to normal by 30 minutes after glucagon administration. Mean glucose values at 60 minutes and beyond were higher with GlucaGen than with pancreatic glucagon.

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Study 8 (007/Denmark) compared efficacy of IM glucagon to iv glucose in treating spontaneous hypoglycemia in patients with blood glucose of 3.0 mm or lower. The primary efficacy variable was time to recovery which ranged (b)(4) with glucagon and (b)(4) for intravenous glucose.

Study 9 (153/UK) was conducted in 10 patients with type 1 diabetes who were given insulin to induce hypoglycemia. GlucaGen was given intramuscularly. Prior to injection mean plasma glucose was 4.71 mg/dl and was 6.53 at the time of injection. At 5, 10, 15, and 20 minutes, mean glucose values were 131, 155, 171, and 152 respectively.

Studies 10, 11 and 12 were conducted in Denmark and were reported also to show increases in plasma glucose after intramuscular injection of GlucaGen. The details were not reviewed.

Gastrointestinal Examinations:

reproduced from NDA p19-20 vol 12

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3.4 Gastrointestinal Examinations/Other Diagnostic Procedures

Four clinical trials, studies 13-16 (020, 025, 026, and 027, respectively), were conducted in Japan to evaluate the usefulness and safety of glucagon (rDNA) as premedication for upper gastrointestinal endoscopy and radiological examination.

The largest study (14, 025/Japan) was a double blind, parallel group comparison of glucagon (rDNA) to pancreatic glucagon in 192 patients undergoing radiological exams. Glucagon

(rDNA) or pancreatic glucagon (1 mg/ml in sterile water) was injected *im* prior to gastrointestinal exams and the efficacy was evaluated by the physician based on secretion of barium from stomach to small intestine, gastric peristalsis, tension of duodenum, and change of gastric mucosa. There was no difference in the effectiveness of glucagon (rDNA) compared to pancreatic glucagon. Treatment was rated effective in 66.4% of the 95 patients injected with glucagon (rDNA) and in 65.9% of 97 patients injected with pancreatic glucagon.

In studies 15 and 16, the effect of glucagon (rDNA) as a pretreatment for upper gastrointestinal tract endoscopy was evaluated. In study 15 (026/Japan), the effect of 1 mg/ml glucagon (rDNA) was compared to that of 1 mg/ml pancreatic glucagon. Efficacy was evaluated by physician assessment of difficulty of observation and gastric peristalsis at 5 minutes and final time. Treatment was considered effective in 39 (78%) out of 50 patients injected with glucagon (rDNA), and 45 (92%) of 49 patients injected with pancreatic glucagon. In study 16 (027/Japan), the efficacy of 0.5 mg and 1.0 mg glucagon (rDNA) injected either *iv* or *im* was investigated. There was no difference between the two routes of administration, with treatment rated as effective in 92.3% of the 65 patients after *im* injection and 87.9% of the 33 patients receiving glucagon (rDNA) *iv*.

In study 13 (020/Japan), similar efficacy rates were found in patients injected with glucagon (rDNA), either 0.5 mg *iv* or 1.0 mg *im*, prior to undergoing radiologic (40 patients) or endoscopic (42 patients) examination. Treatment was considered effective in 80% of patients undergoing radiologic and 95% of patients undergoing endoscopic examinations.

Adverse Events:

Reports of the 18 studies described previously are shown in the table. Healthy volunteers reported more adverse events than did patients but there appeared to be little difference between GlucaGen and pancreatic glucagon. There were six spontaneous reports of adverse events from September 1989 through March 1989. Two were lack of (or decreased) efficacy. The others were abnormal number of white cells, exanthema, headache, and vomiting.

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Glucagon (rDNA)

Treatment	Healthy Volunteers		Patients	
	Pancreatic	Glucagon (rDNA)	Pancreatic	Glucagon (rDNA)
Total Number of Subjects	56	164	177	438
Types of AEs	n (%)	n (%)	n (%)	n (%)
Nausea	29 (52%)	46 (28%)	23 (13%)	45 (10%)
Dizziness	14 (25%)	21 (13%)	0	0
Vomiting	2 (3.5%)	6 (3.6%)	0	0
Headache	6 (11%)	4 (2.4%)	0	0
Generally unwell/malaise	1 (1.7%)	2 (1.2%)	0	0
Hypoglycemia	0	0	2 (1.1%)	2 (0.5%)
Hyperglycemia	0	0	0	1 (0.25%)
Death	0	0	0	2 (0.5%)
Other	11 (20%)	21 (13%)	3 (1.7%)	6 (2%)

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Antigenicity:

Study 12 (078/Denmark) was a parallel comparison of GlucaGen and pancreatic glucagon in 66 healthy volunteers. They received glucagon at 0 and 6 weeks and had antibodies measured at 0, 6, and 12 weeks. Sera were assayed against IgG antibodies for yeast contaminants and compared to a reference range from sera from 216 healthy volunteers. No increase in antibody titers were seen after treatment of either glucagon. Studies 17 and 18 (071 and 072/Denmark) were performed in patients with diabetes who received intravenous glucagon to stimulate pancreatic C peptide release. This is a standard test to distinguish type 1 from type 2 diabetes. Patients were randomized to an initial test with either GlucaGen or pancreatic glucagon done in random order 1 to 7 days apart. Patients received a second test using GlucaGen 3-6 months later. Therefore ALL patients received two injections of GlucaGen and one injection of pancreatic glucagon. No differences were observed between the two glucagon preparations with respect to C peptide secretion or elevation of blood glucose. As shown in the table, no change in antibody titer was observed.

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Study Treatment	DK/MIS/071/MIS		DK/MIS/075/MIS		DK/MIS/078/MIS	
	Pancreatic	Glucagon (rDNA)	Pancreatic	Glucagon (rDNA)	Pancreatic	Glucagon (rDNA)
No. Patients	22	21	7	14	21	42
Visit 1*	0.341	0.309	0.614	0.546	0.39	0.275
Visit 2	0.337	0.286	0.577	0.511	0.388	0.274
Visit 3	0.353	0.318	0.546	0.511	0.382	0.267

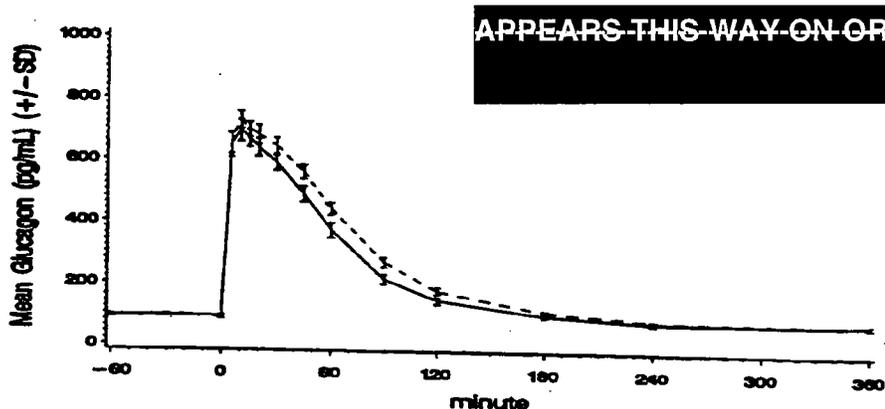
*Visit 1 = 0 week, Visit 2 = 3 months (071)/6 weeks (075 and 078), Visit 3 = 6 months (071)/12 weeks (075 and 078)

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Bioequivalency with Glucagon USP from Eli Lilly - 006/USA

This was a cross over study in 32 healthy volunteers who received 1 mg intramuscular GlucaGen vs glucagon USP (Eli Lilly) in random order with a washout of 2-10 days. Blood samples were obtained from 60 minutes before and 360 minutes after injection. 100 gms of glucose was ingested at 180 minutes after injection to suppress secretion of endogenous glucagon.

Mean Glucagon Concentration Profile - 2X2 Cross Over



BEST-POSSIBLE

— GlucaGen — Glucagon USP
 - - - Glucagon USP - - - GlucaGen

As shown in the figure, plasma glucagon levels rose rapidly after injection and there was little difference between GlucaGen and glucagon USP.

PK parameter	GlucaGen(GlucaGen)	pancreatic Glucagon
AUC, mean (SD)	69150 (21020)	77796 (18460)
Cmax, pg/ml	726 (227)	769 (165)
Tmax, min	13.2 (8.1)	12.2 (5.8)

The two preparation met criteria for bioequivalence. Still, the AUC and Cmax were about 10% lower with GlucaGen vs pancreatic glucagon. However this difference was not present if only data on dosing day 1 were used (see below). The reason for this carry-over effect is not clear.

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Table 8-2: Glucagon - Treatment Comparison

PK Parameter	Ratio or Difference	P-Value	Lower 90% C.I.	Upper 90% C.I.
AUC ₀₋₃₆₀ (Glucagen/Glucagon USP)	0.880	0.005	0.82	0.95
C _{max} (Glucagen/Glucagon USP)	0.932	0.043	0.88	0.99
T _{max} (Glucagen - Glucagon USP)	0.000	0.447		

P-value and 90% CI for between group comparison of AUC₀₋₃₆₀ and C_{max} were calculated from ANOVA based on the crossover model, using log-transformed data.

For T_{max}, the differences between test and reference groups were estimated as the median of the differences within each subject, using raw data. P-values were calculated using Signed Rank test.

Data Source: End-of-Text Table 7a.

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Table 8-3: Glucagon - Treatment Comparison for dosing Day 1 only

Parameter	Ratio	P-Value	Lower 90% C.I.	Upper 90% C.I.
AUC ₀₋₃₆₀ (Glucagen/Glucagon USP)	1.048	0.587	0.91	1.21
C _{max} (Glucagen/Glucagon USP)	1.053	0.507	0.92	1.20
T _{max} (Glucagen - Glucagon USP)		0.783		

P-value and 90% CI for between group comparison of AUC and C_{max} were calculated from ANOVA with treatment, sex, and treatment by sex interaction as factors, using log transformed data.

For T_{max}, p-values were calculated using ANOVA on rank statistics.

Data source: End-of-text Table 8.

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With respect to plasma glucose levels, both preparations gave the same result as shown in the figure below. C max was 152 mg/dl in both preparations which occurred at 28.8 minutes after GlucaGen and 31.5 minutes after glucagon USP.

Mean Glucose Concentration Profile - 2x2 Cross Over

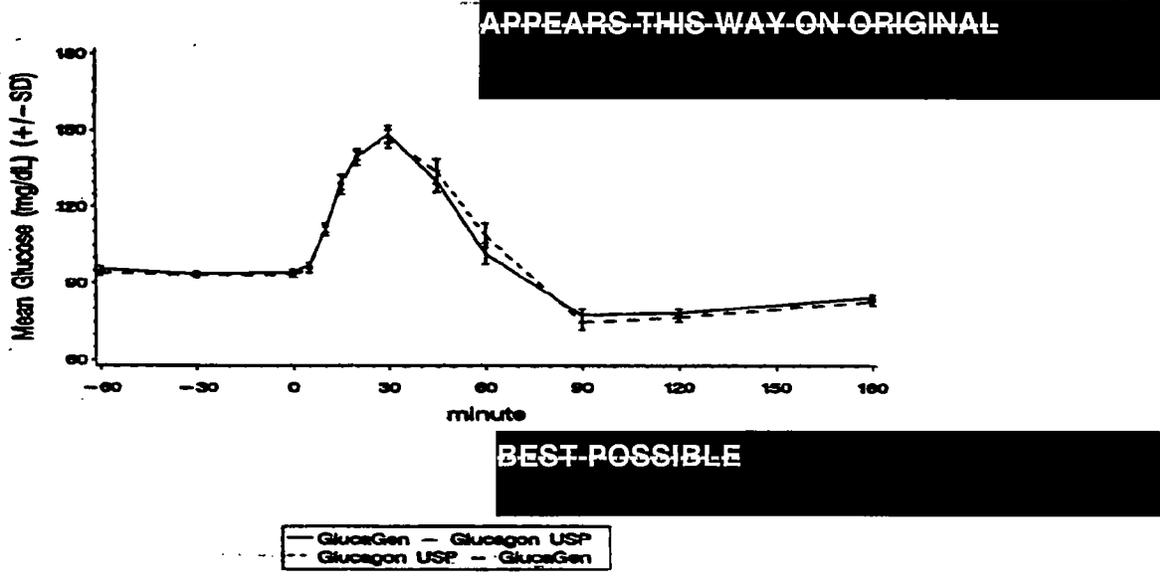


Table 8-4: Glucose Parameters

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PK Parameter	n	GlucaGen		n	Glucagon USP	
		Mean	SD		Mean	SD
AUC (mg)	36	17455.07	1784.49	36	17256.39	1993.23
C _{max} (mg/ml)	36	152.17	19.36	36	152.42	19.30
T _{max} (min)	36	28.75	5.90	36	31.53	9.09

Data Source: Table 7a.

Adverse events were the same with both preparations. 12 subjects reported 21 events after GlucaGen and 11 subjects reported 19 events after pancreatic glucagon. None were severe. Most frequent events among 38 subjects were:

Event	GlucaGen NOVO	Glucagon-USP Lilly
nausea	5	8
dizziness	5	4
vomiting	2	4

Critique:

Although the data from this study would appear to show that GlucaGen and glucagon USP were bioequivalent, the study suffers from a major technical problem. The C max reported for both glucagon preparations is about 700 pg/ml which is much lower than values of about 4500 pg/ml reported in the foreign studies. From other sources, we know that the higher number is more likely to be correct. The reason for this discrepancy could not be ascertained from material in the original submission and was the basis of an inquiry to Novo-Nordisk on October 2, 1997. (See below). The T max observed in the present study of about 13 minutes for both preparations is consistent with previous reports, and is the most important measurement with respect to clinical usefulness for emergency treatment of hypoglycemia.

The two preparations caused the same rise in plasma glucose. However, since the single dose which was given was supra maximal, it would be fallacious to conclude that the two preparations were bioequivalent on the basis of these results. We know from other sources that doses of intravenous glucagon from (b)(4) give the same result.

Novo-Nordisk submitted a response on December 16 to my query of October 2, 1997. They acknowledge that the C Max of 0.7 ng/ml is substantially below the values of about 4.5 ng/ml found in 1988 (b)(4) at Novo Nordisk Biolabs, and marginally below the value of 1.4 ng/ml found in the 1992 USA study which utilized the same (b)(4) (b)(4) as the present study (see table).

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Study	Year	Administration	Mean Cmax / ng/ml	Assay
000 present study	1997	Intramuscularly	0.7	(b)(4)
001	1992	Intramuscularly	1.4	(b)(4)
015	1988	Intramuscularly	4.4; 5.0	(b)(4)
016	1988	Subcutaneously	6.6	(b)(4)
095	1988	Intramuscularly	2.5	(b)(4) Novo Nordisk
101	1988	Intramuscularly	4.1; 4.4	(b)(4)

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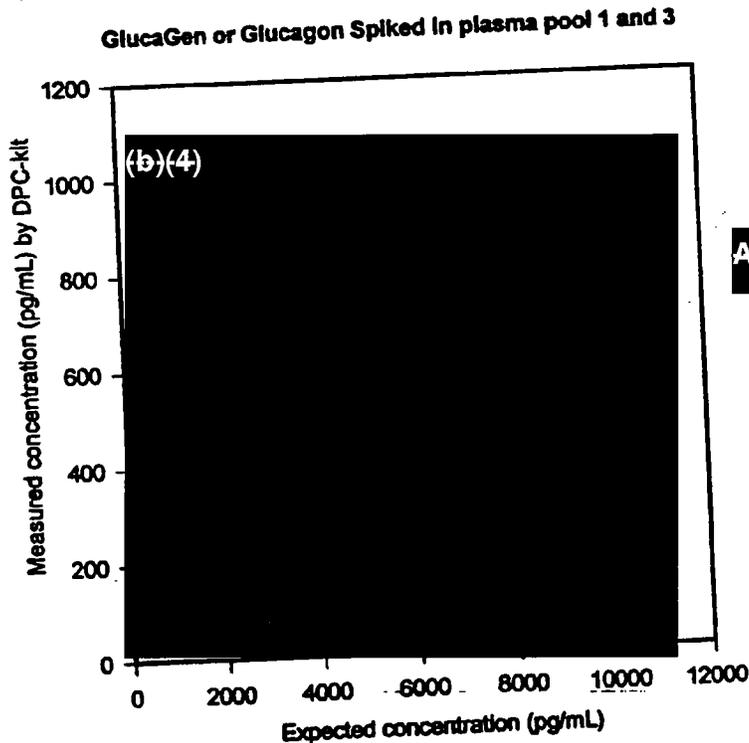
Based on spiking pooled plasma with fresh glucagon, they concluded that the underestimate of the true glucagon value in (b)(4) was due to a "matrix factor" reflecting the different protein contents in the plasma samples and diluent. As shown in the figure, the (b)(4) grossly underestimated values above 500 pg/ml. From these data, they derive an equation which they then used to "correct" values from the original (b)(4). Mean corrected values for C max are 2352 pg/ml for GlucaGen and 2941 pg/ml for Glucagon USP. However, data from the subjects with the three highest glucagon values were excluded because they still exceeded the limits of the correction procedure.

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(b)(4)

where z is "true" glucagon concentration pg/ml and y is the measured glucagon concentration in pg/ml.

The model curve is illustrated in the figure below.



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The (b)(4) used for these samples was designed to measure glucagon levels in clinical samples. Since it was known in advance that the C max following im injection would be about 50x the physiological concentration, appropriate dilutions should have been made so that the samples could be read from the standard curve. That differences in protein content can affect separation of bound from (b)(4) is well known and procedures have been developed to handle this problem. One way would have been to add glucagon-free plasma to the standards.

While it is beyond the needs of this review to go over the Sponsor's correction procedure in great detail, the following comments should suffice to explain why it cannot be accepted as providing an adequate demonstration of bioequivalence:

1 The Sponsor's spiking experiment demonstrates that high values were grossly underestimated, and provides a correction factor for "estimating" this underestimation. The correct values are still not known. This procedure would obscure any potential differences between the two glucagon preparations. Since the very reason the study was done in the first place is to detect such differences, the results of this study, even as corrected, can not be used to establish bioequivalence.

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2 It is not clear why the Sponsor feels the inability to detect high values reflects a matrix problem resulting from differences in the protein content of the samples and standards. To show this, one would have to spike serial dilutions of plasma with a constant amount of added glucagon. What was done was to spike plasma samples with varying amounts of glucagon. I think the most likely explanation for the inability to detect high values was that the amount of antibody in the assay had been exceeded.

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3 The correction procedure is the same for the GlucaGen values as for the Glucagon USP values. How then could the correction procedure detect any differences which were not apparent in the original (uncorrected) data?

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4 Even if one were to accept the correction procedure, the corrected values would still NOT establish bioequivalence. C max and AUC for GlucaGen were both lower than with USP Glucagon. (see table)

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5 The fact that the C max was only 1.4 pg/ml in the previous 1992 US study should provide no solace. The same assay kit was

used then as in the 1996 study (006/USA) and one can presume that the same problem in detecting high values was present. Indeed, the mean value of 1.4 does in fact exclude one subject whose values were too high to measure. Furthermore, commenting on the C max values in the earlier US study, the NDA states on p 14 "These results must be interpreted with caution because the glucagon batch used in this study did not meet all stability specifications."

In summary, the results of Study 006/USA cannot be accepted as a demonstration of bioequivalence, because the glucagon assay was not valid. The correction procedure employed by the Sponsor does nothing to clarify the situation and, if anything, would lead to the conclusion that GlucaGen was less bioavailable than USP Glucagon.

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GLU/D/CD/006/USA

Appendix X

Analysis of PK Parameters - Glucagon Concentration - Treatment Comparison

(Exclude Subject #7 #10 #24)

PK Parameter	Group	n	Mean	SD	Median	Min	Max	Between Group Comparison		
								Ratio Difference	P-value	90% CI
AUC	Glucagon USP	33	104419.74	43734.92	95364.78	32627.34	230624.34	0.788	0.002	(0.70 , 0.89)
	Glucagon USP	33	132657.66	55250.98	121017.85	46237.83	322488.31			
Cmax	Glucagon USP	33	2352.02	1672.31	2066.64	565.53	8471.09	0.768	0.019	(0.64 , 0.92)
	Glucagon USP	33	2941.47	1691.93	2444.23	788.79	8581.36			
Tmax	Glucagon USP	33	13.18	8.27	10.00	5.00	45.00	0.000	0.484	
	Glucagon USP	33	12.27	6.01	10.00	5.00	30.00			
AUC_inf	Glucagon USP	33	111834.84	44540.64	103358.18	34190.14	241815.75	0.798	0.002	(0.71 , 0.89)
	Glucagon USP	33	140298.69	56219.75	135179.68	47834.28	326398.65			

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P-values and 90% CI for between group comparison in AUC, Cmax and AUC_inf were calculated from ANOVA based on the crossover model, using log-transformed data. For Tmax, the differences between test and reference groups were estimated as the median of the differences within each subject, using raw data, the p-values were calculated using Signed Rank test.

Labeling issues

The draft labeling is acceptable except, under "treatment of hypoglycemia" in the DOSAGE and ADMINISTRATION section:

"...however a second or third glucagon injection is not contraindicated. Intravenous glucose must be given should the patient fail to respond to glucagon"

A single dose of glucagon is more than enough to cause a maximal response. If the patient fails to respond to the first dose, it should be assumed that he/she will not respond at all. Therefore the label should be changed to read:

...The dose may be repeated if the patient fails to respond (five minutes after iv or 15 minutes after im glucagon). But emergency assistance should be sought because intravenous glucose MUST be given if the patient fails to respond to the second dose...

This revised wording is more consistent with the recommendations in Reference A - Drug Information for the Health Care Professional: USPDI 1997.

The Sponsor may also wish to include a figure (recovery from hypoglycemia for example) in the clinical pharmacology section.

Finally there should be more discussion of the eight "anaphylactic reactions" which have occurred with GlucaGen. These have generally occurred in association with endoscopic examination. The label should state that patients should be treated with epinephrine if they encounter respiratory difficulties after being given GlucaGen.

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Summary and Recommendations:

The application demonstrates that GlucaGen is safe and effective for its labeled use. Studies conducted outside the United States demonstrated that when given intramuscularly, GlucaGen, was effective treatment for insulin-induced hypoglycemia in diabetic patients and in healthy volunteers. The return to baseline glucose concentration occurs within about 20 minutes which mirrors the peak plasma glucagon concentration which occurs at about 12 minutes. Semiquantitative comparisons of GlucaGen with pancreatic glucagon for gastrointestinal relaxation during radiographic procedures gave equivalent results. No antibody formation was observed either in healthy volunteers or in diabetic patients.

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The comparative study with Lilly USP Glucagon performed in the USA was flawed by failure to adjust the assay procedure to measure the high glucagon values observed after injection. Both preparations showed the same C max but the reported values were less than 20% expected. T max was about 13 minutes for both preparations and both resulted in the same rise in plasma glucose. Thus GlucaGen and Lilly USP Glucagon are therapeutically equivalent but the claim of bioequivalence was not established because the assay technique was not valid.

I recommend that GlucaGen be approved in accordance with the proposed label for use in treatment of hypoglycemia, and to produce gastrointestinal relaxation during radiographic and endoscopic procedures. However, any claim of bioequivalence with Lilly USP glucagon should be rejected.

/s/

APPEARS THIS WAY ON ORIGINAL

Robert I Misbin MD
Medical Officer
January 31, 1998

To do unit room

2/4/98

/s/

Excellent review.

/s/

2/2/98