

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020918

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Labeling Review

NDA 20-918 GlucaGen [glucagon (rDNA origin) for injection]

Date of Submission: June 19, 1998 (physicians and patients package insert)

Date of Review: June 22, 1998

~~APPEARS THIS WAY ON ORIGINAL~~

The June 19, 1998, physicians package insert was compared to our 6/17/98 fax for the draft physicians package insert (FDA revision #6). The sponsor has incorporated all the changes requested by the Agency.

The June 19, 1998, patients package insert was compared to our 6/17/98 fax for the draft patients package insert (FDA revision #2). The sponsor has incorporated all the changes requested by the Agency.

/s/

Julie Rhec, Project Manager

~~APPEARS THIS WAY ON ORIGINAL~~

cc: OrigNDA
HFD-510/DivFile
HFD-510/Misbin/Berlin/Rhec
HFD-870/Shore

Labeling Review

p.s. The sponsor submitted unannotated physicians package insert on 6/22/98. This submission is identical to the 6/19/98 physicians package insert except the annotations removal.

Labeling Review

NDA 20-918 GlucaGen [glucagon (rDNA)]

Date of Submissions: May 1 and 22, 1998

Date of Review: June 5, 1998

Reviewed by: Julie Rhee

BEST-POSSIBLE

The labeling amendments dated May 1 and 22, 1998, were compared with our draft labeling request for physician package insert (FDA revision #4) and patients package insert (FDA revision #1) which were faxed to the sponsor on April 1, 1998.

I. The following changes (other than what we've requested) were noted on the physician package insert dated 5/1 & 5/22/98:

1. Pediatric Use subsection: **APPEARS THIS WAY ON ORIGINAL**

The original labeling submitted with the original NDA stated that safety and effectiveness in pediatric patients have not been established. However, the physician dated 5/1 and 5/22/98 states "The use of glucagon in pediatric patients has been reported to be safe and effective." The sponsor cited four literature articles published between 1955 and 1988 ('55, '58, '64, and '88) in support of this change.

Dr. Misbin, please comment whether or not GlucaGen is safe and effective in pediatric patients. The articles are behind the 5/1/98 tab.

2. ADVERSE REACTIONS section:

"Hypersensitivity reaction" is changed to "Allergic reaction"

Dr. Misbin, is this change acceptable?

3. DOSAGE AND ADMINISTRATION section, "For the treatment of hypoglycemia" subsection:

- i. The first sentence "For adults and for pediatric patients weighing more than 55 lb (25 kg)," has been changed to "For adults and for pediatric patients weighing 55 lb (25 kg) or more,"

This is an editorial change and is acceptable.

- ii. Novo added "younger than" before "6-8 years old" in the first sentence of the second paragraph.

This is an editorial change and is acceptable.

- iii. "Time for GI smooth muscle relaxation" and "Duration of action":

The sponsor changed the units from "USP Units" to "mg (IU)"; but the number of units stayed the same:

Dr. Berlin, please comment whether or not this change is acceptable.

4. HOW SUPPLIED section: ~~APPEARS THIS WAY ON ORIGINAL~~

Dr. Berlin, please comment on this section.

II. The following changes were noted on patients package insert dated 5/1 and 5/22/98:

1. The sponsor added "GlucaGen® [glucagon (rDNA)] Emergency Kit For Diabetic Insulin Reaction" and then "INFORMATION FOR PATIENTS."

Drs. Misbin & Berlin, is this heading acceptable? ~~APPEARS THIS WAY ON ORIGINAL~~

[For your info, Lilly's patients package insert for glucagon states INFORMATION FOR THE USER GLUCAGON FOR INJECTION (rDNA ORIGIN)]

2. Changed "orange juice" to be given to patient to "fruit juice" to be given to patient.

Dr. Misbin, is this acceptable? ~~APPEARS THIS WAY ON ORIGINAL~~

3. In the DIRECTIONS TO PREPARE GLUCAGEN® FOR INJECTION, Step 1, Novo deleted "Clean rubber stopper with alcohol swab." Their reason for this deletion is because there are no alcohol swabs provided with the package and this might cause confusion and delay the injection. However, because the direction does not state the alcohol swab is provided in the package and these are diabetic patients who already have alcohol swabs for insulin injection, I feel the statement should remain.

Dr. Misbin, do you agree? ~~APPEARS THIS WAY ON ORIGINAL~~

4. Novo deleted the statement "Cleanse injection site on buttock, arm, or thigh with alcohol swab" for the same reason mentioned #3. However, again for the same reason, I feel this statement should remain as Step 6 and change the current Step 6 to Step 7.

5. HOW TO TAKE GLUCAGON: ~~APPEARS THIS WAY ON ORIGINAL~~

Novo changed from "Inject all 1 ml (adults and children above 55 lbs or 6-8 years) or . . ." to "Inject all 1 ml (adults and children 55lbs, 6-8 years and above) or . . ."

~~APPEARS THIS WAY ON ORIGINAL~~

This change is acceptable.

APPEARS THIS WAY ON ORIGINAL

6. HOW GLUCAGON WORKS:

On the 4/1/98 fax, we had requested Novo to change "Blood sugar levels increase within 15 minutes of injection" but Novo did not make the change. It reads "Blood sugar levels increase within 10 minutes of injection"

Dr. Misbin, please comment.

APPEARS THIS WAY ON ORIGINAL

7. POSSIBLE PROBLEMS WITH GLUCAGEN® TREATMENT:

In the second sentence, change the word "or" to "and" between "GlucaGen®" and "may experience rapid heart beat for a short while."

8. Carton label:

APPEARS THIS WAY ON ORIGINAL

Dr. Berlin, is the proposed carton label acceptable?

Recommendation:

APPEARS THIS WAY ON ORIGINAL

In lieu of having a labeling meeting, a copy of 5/1 and 5/22/98 amendments along with our 4/1/98 fax have been left with Drs. Misbin, Berlin, HRhee, and Shore for their inputs. Once I receive their comments, I'll incorporate them into the revised labeling (FDA revision #5) and convey to the sponsor.

APPEARS THIS WAY ON ORIGINAL

/s/

Julie Rhee, Project Manager

cc:OrigNDA
HFD-510/DivFile
HFD-510/Misbin/Berlin/HRhee
HFD-870/Shore

Labeling Review

May 11, 1998

Ms. Julie Rhee,
Consumer Safety Officer
Food and Drug Administration
CDER/ODEII/DMEDP/HFD-510
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Novo Nordisk

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~~APPEARS THIS WAY ON ORIGINAL~~

Re: Correction of Labeling Revision 4

Dear Julie,

We noted that in error, we hadn't changed one of the references to dosage to include the 55 lbs. Our draft Package Insert Revision 4, page 9 reads:

For the treatment of hypoglycemia: For adults and for pediatric patients weighing more than 55 lb (25 kg), administer 1 mg by

It should read:

~~APPEARS THIS WAY ON ORIGINAL~~

For the treatment of hypoglycemia: For adults and for pediatric patients weighing 55 lb (25 kg) or more, administer 1 mg by

Please make this change on your hard copy and your electronic copy. ~~APPEARS THIS WAY ON ORIGINAL~~

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,

Mary Ann McElligott, Ph. D.,
Director, Regulatory Affairs

~~APPEARS THIS WAY ON ORIGINAL~~

72687

Use of *Glucagon* TO TERMINATE *Insulin Reactions* IN DIABETIC CHILDREN*

GLUCAGON is a hormone produced by the alpha cells of the pancreatic islets. It produces hyperglycemia by enhancing glycogenolysis in the liver. It has been used intravenously in one reported study to terminate therapeutic insulin shock on a psychiatric ward.

Epinephrine has long been used in therapy of insulin reactions. Glucagon would have the advantage of not possessing a hypertensive effect.

The present report concerns experience with glucagon used to treat mild insulin reactions on a pediatric ward. Glucagon¹ was given *subcutaneously* in a dosage of 0.03 mg./kg. body weight. For purposes of the present observations, the attendants refrained from administering carbohydrate for one hour following the administration of the glucagon. Capillary blood was used for patient R.F. Venous blood was obtained

G. E. GIBBS; D. W. EBERS, and
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before breakfast, and ranged from 10 to 80 units, adjusted by a plan of flexible insulin dosage². His diet contained approximately 1200 calories and included between-meal and bedtime snacks. On 5-21, his hypoglycemia was manifested by unconsciousness; on 5-28, he was merely drowsy and irritable. (See Table I).

CASE II

A.K. was a 10-year-old girl with diabetes complicated by hyperthyroidism. She was admitted to the University of Nebraska Hospital on 5-14-57. Her diabetes was of three years' duration. During these studies, she was receiving

TABLE I
EFFECT OF SUBCUTANEOUS GLUCAGON ON
BLOOD SUGAR

Patient	Date	Before Glucagon	Blood Sugar mg./100 ml. 15 min.	30 min.	60 min.	Comment
R.F.	5/21	20	41	54	54	Responded clinically within 5 min.
	5/28	80	127	82	80	Responded within 10 min.
A.K.	5/29	55	79	—	110	Responded within 10 min.
	5/31	72	140	190	187	
	7/24	41	111	156	123	Felt better within 10 min.
	7/29	40	112	170	160	Felt better within 10 min.
	8/3	170	268	300	268	No improvement in symptoms

from patient A.K. Blood sugar was determined by the Benedict method after preparation of a tungstic acid filtrate.

CASE I

R.F. was a 25-month-old boy with diabetes of one week's known duration when admitted to the University of Nebraska Hospital on 4-27-57. He was receiving a mixture of Semi-Lente and Ultra-Lente insulins in a ratio of 3 to 1. His total daily insulin dosage was given

propylthiouracil in preparation for subtotal thyroidectomy. On the first four tests, hypoglycemia was suspected because of dizziness. The total daily insulin dosage of ordinary Lente was given before breakfast. Insulin dosage ranged from 24 to 44 units. Her diet contained approximately 2500 calories. The study on 8-3 was two days post-thyroidectomy. At that time, she was having some respiratory difficulty and complained of dizziness. This was interpreted clinically as hypoglycemia, but

*Article received for publication October 14, 1957.

Nebraska State Medical Journal 1958; 43:

the blood test later showed that her blood sugar was actually elevated. The glucagon, however, caused a further rise.

SUMMARY

Subcutaneous injection of glucagon provides a convenient means of treatment of insulin hypoglycemia in the diabetic child.

REFERENCES

1. Schulman, J. L., and Greben, S. E.: Effect of Glucagon on the Blood Glucose Level and the Clinical State in the Presence of Marked Insulin Hypoglycemia. *J. Clin. Inv.*, 36:74, 1957.
2. Glucagon, Lilly, 1 mg. per ml., Batch C T 871.
3. Gibbs, G. E.: A Study in Out-Patient Management of Juvenile Diabetes. *Nebr. State M.J.*, 40:399, 1955.

TUBERCULOSIS ABSTRACTS

ADVANTAGES OF HOSPITAL ADMISSION CHEST X-RAY EXAMINATIONS

Routine hospital admission chest X-ray examinations are performed in only 21% of all hospitals in the United States according to the 1954 figures of the American Hospital Association. It is difficult to comprehend the reason for such a situation when the advantage of such examinations was demonstrated as long as 20 years ago. For many reasons chest X-ray examinations should be a necessary and integral part of a patient's studies in the hospital.

Communicable Diseases — Routine chest X-ray examination of the hospital population is important to all hospital personnel and to their families. The incidence of tuberculosis and other respiratory diseases is said to be greater among hospital personnel than among workers in any other industry. In any hospital chest X-ray program preemployment and at least annual chest X-ray examinations of employees are essential. The making of semi-annual chest X-ray films of those on the attending and house staffs is also inherent in such programs.

Errors in Diagnosis of Chest Diseases — The value and necessity of admission chest X-ray examination were demonstrated over 20 years ago when it was proved that, as a group, the physicians at the University of Michigan Hospitals committed one gross error a day without the benefit of such chest X-ray films. This demonstration in itself warrants the adoption of routine admission chest X-ray examination of all hospital patients.

Unsuspected Cases of Chest Disease — Many unsuspected cases of chest disease amenable to treatment are uncovered by admission chest X-ray examination. Prompt treatment of these patients decreases morbidity and mortality rates and the length of hospitalization. In this day of high hospital costs and shortages of hospital beds the latter consideration is not a minor one.

Preoperative Work-up — In the evaluation and preparation of the surgical patient, the routine ad-

mission chest radiograph furnishes information of value to surgeons and anesthesiologists. The correlation of the physical findings with the X-ray findings increases the accuracy of the appraisal of the patient's cardiopulmonary status and often influences the choice of the anesthetic agent and type of surgical procedure.

Record of Chest Condition — In everyday roentgenography of the chest, we are faced with the problems of ascertaining, if possible, the acuteness or chronicity of thoracic abnormalities. Many such questions can be resolved promptly and easily if previous chest films are available for comparison. Admission chest X-ray films provide such valuable records, particularly in patients with postoperative and other types of thoracic complications. X-ray diagnosis of chest disease is thus made more reliable and accurate.

Life History of Disease — Over 20 million patients are admitted to hospitals annually. Chest X-ray examination of all such patients would, not only provide information of immediate importance to the patient but also valuable data for the study of the natural history of many chest diseases. The potentialities of the use of such data in the study of primary cancer of the lung has been demonstrated.

Compensation and Accident Cases — In accident and compensation cases, as in other types of medical practice, negative and positive findings are of equal importance. The availability of a routine roentgenogram provides essential data for the treatment of the patient and in the consideration of compensation claims. Unexpected traumatic lesions of the chest and adjoining tissues which may not produce immediate symptoms are not infrequently uncovered by admission chest X-ray films.

Trauma to other parts of the body may often be suspected or indicated on the basis of intrathoracic changes. For example, basilar atelectatic foci might reflect injury to intra-abdominal and/or diaphragmatic structures.

Teaching Program in General Hospitals — Survey chest X-ray films provide the members of the house staff with an opportunity to become acquainted with the appearance of the average or "normal" chest film, and provide a check on the physical findings. From such correlations the house staff members learn the limitations of the various forms of examination and the indications for further X-ray investigation. A chest X-ray admission program may help to make the hospital an educational center for detection, diagnosis, treatment and even follow-up of chest diseases.

Routine Hospital Examinations — Chest X-ray screening of hospital patients reveals significant positive abnormalities in 10 to 15% of patients. Granted that the presence of many of these abnormalities is suspected, but the severity or extent of disease and/or reactivation of previous disease is very often unsuspected. The percentage of significant positive findings disclosed by admission chest X-ray examination is greater than that revealed by any other routine hospital laboratory procedure.

Detection of Tuberculosis — The great strides made in the treatment of tuberculosis have given

(Continued on page 61)

BEST POSSIBLE

CLINICAL STUDIES WITH GLUCAGON IN CHILDREN

MERRILL J. CARSON, M.D., AND RICHARD KOCH, M.D.*

LOS ANGELES, CALIF.

THE observation by Murlin and associates¹ in 1922 of transitory hyperglycemia immediately following intravenous administration of certain pancreatic extracts led to discovery of the hyperglycemic-glycogenolytic factor of the pancreas termed glucagon. Bürger and associates² demonstrated that glucagon is a protein polypeptide, chemically closely allied to crystalline insulin, and that hyperglycemia results from a direct glycogenolytic action in the liver. In 1953, Stubb and associates³ succeeded in purifying and crystallizing glucagon. It is the purpose of this paper to present our observations on the effects of glucagon in thirty-four children, consisting of a control group and patients with liver disease, glycogen storage disease, and spontaneous hypoglycemia.

PROCEDURE

The clinical material consisted of sixteen normal subjects, eight with liver disease, six with glycogen storage disease, and four with spontaneous hypoglycemia. They ranged from 2 months to 13 years in age. There were sixteen males and eighteen females.

Glucagon† was supplied in 10 c.c. vials which were constantly refrigerated. The solution contained 0.95 mg.

From the Department of Pediatrics, University of Southern California School of Medicine, and the Los Angeles Children's Hospital.

This material, in part, was presented to the Western Society of Pediatric Research in Los Angeles, Calif., on Nov. 20, 1954.

*Trainee in metabolic diseases, supported by the United States Public Health Department.

†Generously provided by Eli Lilly and Company, Indianapolis, Ind.

of glucagon per cubic centimeter (Lot No. 208-158B-214) and the standard dose used for all tests was 20 μ g per kilogram of body weight. All subjects were fasted overnight, and two to three days elapsed between tests. Blood sugar determinations were done by the micrometric method on capillary blood, using a modified Folin-Wu technique.*

NORMAL SUBJECTS

Table I shows that glucagon produced consistent blood sugar elevation ranging from 22 to 68 mg. per cent, with an average of 54 mg. per cent, thirty minutes after subcutaneous drug administration. The average one-hour blood sugar level was 26 mg. per cent with only Case 9 showing a value below the fasting value. Three subjects studied in greater detail showed that the peak effect of subcutaneously administered glucagon occurred between twenty and thirty minutes after injection, with substantial elevation within ten minutes.

The standard dose (20 μ g per kilogram) was doubled and the hyperglycemic results of the 20 and the 40 μ g per kilogram dosage compared in Fig. 1, which shows that this increase in dosage did not increase the hyperglycemic response. Our data are in agreement with the work of Louve and co-workers⁴ who were also unable to show increased hyperglycemic effect with increased dosage. Both adrenocorticotrophic hormone and Adrenalin

*Folin, J.: J. Biol. Chem. 86: 173, 1930.

increased the potency of the hyperglycemic effect of glucagon. In Fig. 2, the blood sugar response in the same subject is compared, following glucagon, Adrenalin, and combined Adrenalin-glucagon administration.

twice the peak value obtained with each drug individually, and lasted longer than with either drug alone. Glucagon did not inhibit cardiovascular effects of Adrenalin, such as tachycardia or vasoconstriction.

TABLE I. CONTROL TOLERANCE TESTS IN SIXTEEN SUBJECTS, USING 20 μ G PER KILOGRAM OF GLUCAGON, SUBCUTANEOUSLY, WHICH SHOW AN AVERAGE BLOOD SUGAR ELEVATION OF 64 AND 25 MG. PER CENT AT THE THIRTY- AND SIXTY-MINUTE INTERVALS, RESPECTIVELY

CASE NO.	AGE YR.	BLOOD SUGAR CONCENTRATION, MG. PER CENT			
		FASTING	TIME AFTER DOSE		
			30 MIN.	60 MIN.	120 MIN.
1	1	63	119	105	81
2	1	47	69	63	53
3	2	42	95	88	61
4	2	81	143	110	95
5	3	115	100	172	118
6	1	100	149	122	97
7	5	68	128	93	73
8	5	47	155	102	78
9	5	49	153	60	61
10	6	131	173	137	96
11	8	92	159	149	-
12	8	95	149	111	97
13	8	33	156	136	66
14	12	105	146	108	108
15	12	100	158	127	95
16	13	39	105	89	61

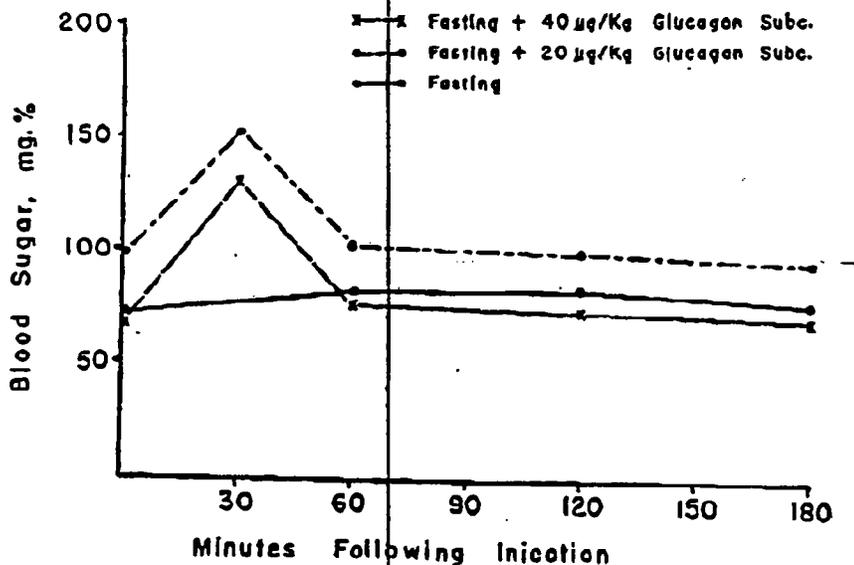


Fig. 1.—Glucagon tolerance curves with subcutaneous 20 and 40 μ G per kilogram doses, showing no additive hyperglycemic effect with increased dosage.

Following simultaneous Adrenalin and glucagon administration, the maximum hyperglycemia was approximately

The anti-insulin effect of glucagon was studied in seven subjects. Fig. 3 illustrates typical curves obtained in

four subjects who had been given 0.25 unit of subcutaneous insulin per kilo-gram of body weight prior to glucagon administration. Within thirty minutes after insulin injection, the blood sugar dropped 26, 21, and 20 mg. per

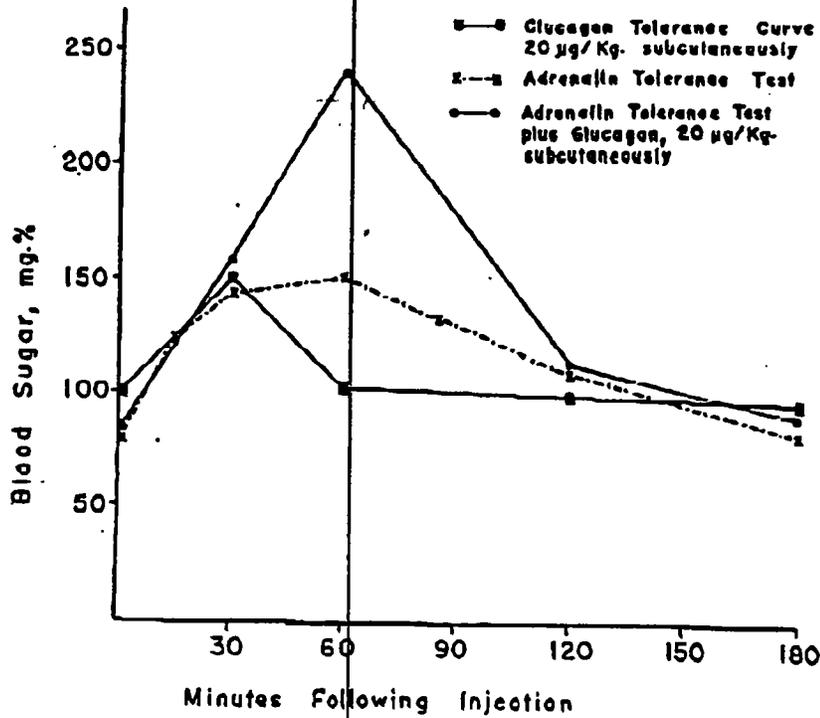


Fig. 2.—The hyperglycemic effect of glucagon, 20 µg per kilogram subcutaneously, is additive to the hyperglycemic effect of simultaneously administered subcutaneous Adrenalin.

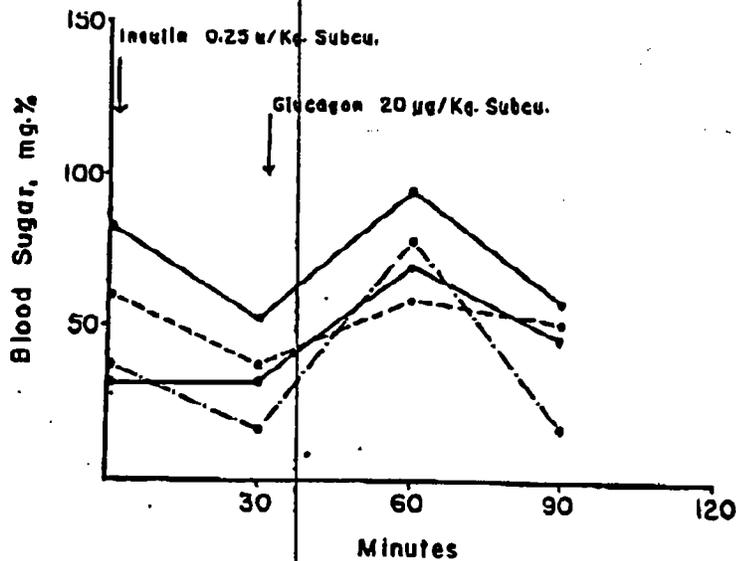


Fig. 3.—Insulin-glucagon tolerance curves demonstrating the anti-insulin effect of glucagon when administered thirty minutes after insulin.

cent, respectively, in three patients, remaining unchanged in the fourth. Glucagon (20 μ g per kilogram) was then given subcutaneously, and within thirty minutes a 35 to 40 mg. per cent increase in blood sugar concentration was noted in all four subjects.

Insulin tolerance tests were performed on three subjects for comparison with combined insulin-glucagon tolerance tests. In the latter, both drugs were administered simultaneously. The results, listed in Table II, illustrate that glucagon was able to counteract the hypoglycemic action of

the effect of glucagon in eight patients with liver disease. In all but one patient, the diagnosis was established by surgical biopsy. Cases 1, 2, and 3 had biliary atresia with cirrhosis; Case 4 had cirrhosis of unknown etiology; Case 5 had a hamartoma replacing most of the liver, associated with hepatic insufficiency; Case 6 had inspissated bile syndrome without cirrhosis; Case 7 had acute hepatitis; and Case 8 had an undiagnosed hepatomegaly. In Case 8 liver biopsy revealed increased glycogen stores, but a definite diagnosis of glycogen storage disease

TABLE II. COMPARISON OF GLUCAGON, INSULIN, AND INSULIN-GLUCAGON TOLERANCE TESTS, USING 20 μ g PER KILOGRAM OF GLUCAGON AND 0.25 UNIT PER KILOGRAM OF INSULIN, SUBCUTANEOUSLY, SHOWING THAT GLUCAGON COUNTERACTS INSULIN-INDUCED HYPOLYCEMIA

CASE NO.	TOLERANCE TEST	BLOOD SUGAR			
		FASTING	RISE OR FALL AFTER TEST DOSE, MG. PER CENT		
			30 MIN.	60 MIN.	120 MIN.
18	Glucagon	88	68	48	-22
7	Glucagon	66	60	25	5
16	Glucagon	59	46	30	2
13	Insulin	86	-19	-19	-7
7	Insulin	100	-17	-12	-22
16	Insulin	88	-2	-17	-21
13	Insulin-glucagon	91	+19	-99	-38
7	Insulin-glucagon	89	+32	-23	-28
16	Insulin-glucagon	93	+37	-14	-23

insulin. In the control insulin tolerance tests, a drop of 19, 17, and 2 mg. per cent, respectively, was noted thirty minutes after insulin administration. When glucagon was given simultaneously with insulin, the tests resulted in a 19, 32, and 37 mg. per cent rise at thirty minutes. The one- and two-hour blood sugar levels in the glucagon-insulin tolerance tests were slightly lower than those in the insulin tolerance tests.

PATIENTS WITH LIVER DISEASE

Since glucagon produces hyperglycemia by glycogenolysis of liver glycogen,⁵ it was of interest to observe

could not be established. The Adrenalin tolerance test in this latter case was normal and there was no associated hypoglycemia or acetonuria. Table III shows that the four subjects with hepatic cirrhosis and the subject with hepatic insufficiency due to replacement of liver tissue by hamartoma cells had from 13 to 24 mg. per cent hyperglycemic response to glucagon administration. The remaining three with inspissated bile syndrome, acute hepatitis, and undiagnosed hepatomegaly had 41, 47, and 28 mg. per cent blood sugar elevation, respectively. The patients with inspissated bile syndrome and acute hepatitis responded norm-

ally in spite of rather severe icterus, well known that the Adrenalin tolerance test in this disease usually shows a flat curve. Since Adrenalin and with serum bilirubin levels of 14 and 8 mg. per cent, respectively.

TABLE III. GLUCAGON TOLERANCE TESTS IN EIGHT PATIENTS WITH LIVER DISEASE, USING THE STANDARD DOSE OF 20 µg PER KILOGRAM, SUBCUTANEOUSLY, SHOWING THE IMPAIRED HYPERGLYCEMIC RESPONSE IN FIVE PATIENTS AND A NORMAL RESPONSE IN THREE OTHERS

CASE NO.	AGE (YR.)	WEIGHT (KG.)	DIAGNOSIS	BLOOD SUGAR, MG. PER 100 ML., MIN. AFTER DOSE				
				FASTING	30 MIN.	60 MIN.	120 MIN.	180 MIN.
1	½	5	Biliary atresia with cirrhosis	105	118	92	98	110
2	1	7	Biliary atresia with cirrhosis	67	85	74	69	67
3	½	6	Biliary atresia with cirrhosis	72	90	72	69	62
4	8	30	Hepatic cirrhosis	55	57	70	53	80
5	12	30	Hamartoma	55	65	70	60	65
6	½	3	Inspissated bile syndrome	87	128	92	82	--
7	7	25	Acute hepatitis	90	137	95	90	--
8	1	8	Hepatomegaly undiagnosed	93	121	109	102	84

TABLE IV. COMPARISON OF ADRENALIN AND GLUCAGON TOLERANCE TESTS IN SIX PATIENTS WITH GLYCOGEN STORAGE DISEASE, SHOWING VARIABLE HYPERGLYCEMIC RESPONSE TO ADRENALIN OR GLUCAGON ADMINISTRATION

CASE NO.	PATIENT	AGE (YR.)	BLOOD SUGAR TIME IN MINUTES AFTER DRUG INJECTION				
			FASTING	30 MIN.	60 MIN.	120 MIN.	180 MIN.
<i>Adrenalin Tolerance Test: ½ minim/kg., subcutaneously</i>							
1	C. S.	2	53	55	65	74	55
2	T. S.	9	40	39	40	44	46
3	J. S.	8	73	74	92	93	--
4	K. H.	7	53	62	70	90	53
5	D. B. (Danniel)	7	94	154	157	132	126
6	D. B. (Dennis)	7	87	126	180	111	114
<i>Glucagon Tolerance Test: 20 µg/kg., subcutaneously</i>							
1	C. S.	2	55	90	80	60	55
2	T. S.	9	32	26	26	42	61
3	J. S.	8	83	71	70	70	58
4	J. S. (I. V.)	8	69	79	77	69	87
5	K. H.	7	59	89	86	64	--
6	D. B. (Danniel)	7	89	96	148	103	--
6	D. B. (Dennis)	7	81	89	89	89	--

Cases 1 and 2 were referred to us for study by Henry G. Kurz, M.D., La Habra, Calif.
 Case 3 was referred to us for study by Paul Starr, M.D., Pasadena, Calif.
 Case 4 was referred to us for study by James N. Yamazaki, M.D., Los Angeles, Calif.
 Cases 5 and 6 were referred to us for study by Vincent Rounda, M.D., Redondo Beach, Calif.

PATIENTS WITH GLYCOGEN STORAGE DISEASE

Cori and Cori⁶ have shown that several types of glycogen storage disease exist. They have shown a specific deficiency of glucose-6-phosphatase in two cases⁶ and structural abnormalities of the glycogen⁷ in two others. It is

glucagon both cause glycogenolysis of liver glycogen by increased phosphorylase activity,⁸ it is reasonable to assume that the hyperglycemic effect of glucagon would be absent in the patients with this disease. Six patients were accordingly tested with the standard dose of 20 µg per kilogram of

glucagon and the results of this test were compared with those obtained with standard Adrenalin tolerance tests. Table IV shows the low Adrenalin tolerance tests in Cases 1, 2, 3, and 4. Case 1, the sibling of Case 2, has clinical signs and symptoms of glycogen storage disease, although liver biopsy has not been performed. Case 2 has been studied by Illingworth and Cori⁷ and shown to have normal liver glycogen. Unfortunately, not enough liver tissue was secured for determination of glycogen content of liver tissue, or for specific enzyme studies. Cases 3 and 4 have clinical signs and symptoms of the disease, as manifested by

phatase activity. Table V shows that Cases 1, 4, and 5 had a 35, 30, and 59 mg. per cent response to glucagon administration, whereas Cases 2, 3, and 6 failed to reveal any hyperglycemic response to glucagon. Case 3 was also given intravenous glucagon without hyperglycemic response.

PATIENTS WITH SPONTANEOUS HYPOGLYCEMIA

It is currently believed that patients with idiopathic hypoglycemia are unable to mobilize enough blood sugar to relieve their symptoms during a hypoglycemic convulsive episode. Glucagon, however, is able to mobilize

TABLE V. GLUCAGON TOLERANCE TESTS IN SIX PATIENTS WITH SPONTANEOUS HYPOGLYCEMIA USING 20 μ G. PER KILOGRAM OF GLUCAGON, SURCITANOLISILY, AND COMPARING THE HYPERGLYCEMIC RESPONSE BEFORE AND AFTER THE INSTITUTION OF ADRENOCORTICOTROPHIC HORMONE AND HYDROCORTISONE THERAPY

CASE NO.	AGE (YR.)	BLOOD SUGAR VALUES, MG. PER 100 ML., MINUTES AFTER DRUG INJECTION				
		FASTING	30 MIN.	60 MIN.	120 MIN.	180 MIN.
1	1½	65	127	97	42	47
2	4	58	100	72	68	--
3	4	69	132	69	69	64
4	2	69	95	53	53	...
<i>One week after ACTH therapy</i>						
1	1½	65	132	115	91	90
2	4	60	165	81	62	84
2	4	90	138	110	100	--
<i>One week after hydrocortisone therapy</i>						
4	2	92	114	95	80	--

hepatomegaly, poor growth, acetonuria, flat Adrenalin tolerance tests, and surgical biopsies, showing increased glycogen stores by histologic methods, but not by chemical determination. Cases 5 and 6 are fraternal twins studied by Illingworth and Cori⁷ and shown to have normal liver glycogen. Glycogen determinations in these two cases were 14.2 and 12.7 per cent, respectively, compared to control values of 0.56 to 4.6 per cent.⁸ Cori and Cori⁸ studied a biopsy specimen obtained from Case 6 and showed a marked reduction in glucose-5-phos-

glycogen stores and raise the blood sugar even in the presence of exogenous insulin. From this, it was postulated that glucagon might be able to counteract the acute hypoglycemic episodes which characterize this disease.

Four patients with idiopathic hypoglycemia were studied. The diagnosis in each was based upon the clinical and laboratory observations of repeated episodes of spontaneous hypoglycemia and abnormal sensitivity to exogenous insulin, as demonstrated by insulin tests. Table V shows that glucagon tolerance tests in these patients

produced an initial, normal hyperglycemic response at the thirty-minute interval. At the two-hour interval, the blood sugar concentration had returned to or below the original fasting level. After the patients were placed on adrenocorticotrophic hormone, 1 mg. per kilogram per day of the gel form, the initial hyperglycemic response was prolonged. In subsequent insulin tolerance tests, neither a single dose of glucagon nor steroid therapy completely protected these patients from the hypoglycemic effect of insulin. However, multiple doses of glucagon have been successfully used to terminate hypoglycemic convulsions in these patients.

DISCUSSION

Glucagon is a polypeptide differing from insulin primarily in its amino acid content.⁹ Methionine and tryptophane are present in glucagon but not in insulin. Cystine, isoleucine, and proline are present in insulin but not in glucagon. The drug is readily utilized subcutaneously and is also effective when given intravenously. It is relatively nontoxic in the dosage used in our studies.

Glucagon has been found in pancreatic extracts of a variety of animals.¹⁰ Its distribution in the pancreas is similar to that of islet tissue in that it is more abundant in the tail of the pancreas and in the fetal pancreas. Pancreatic duct ligation or alloxan administration does not change the gland's glucagon content.¹¹ Fadden and Read,¹² in 1954, showed that S-tythalin A (dexamethylenediguandine) produces vacuolization in the alpha cells of the pancreas and that extracts from pancreas treated in this manner do not contain glucagon. These ob-

servations lend support to the theory that the alpha cells of the pancreas are the site of glucagon production.

Specific glucagon action is thought to be mediated by increased phosphorylase activity, which makes more glucose-1-phosphate available for glucose production¹³ (see Fig. 4). As little as 10 μ g produces a significant elevation of blood sugar concentration.¹¹ Further proof that the site of action of glucagon is in the liver is furnished by hepatic vein catheterization studies which showed that glucagon administration results in a prompt increase of hepatic vein glucose, as compared with peripheral blood glucose values.¹⁴ In addition, glucagon has no hyperglycemic effect in the hepatectomized animals¹⁴ or the eviscerated rat.¹⁵ In contrast to Adrenalin, glucagon has little if any effect on muscle glycogen.¹⁶ Glucagon and Adrenalin also differ in the glycogenolytic response to dihydroergotamine which is an adrenergic blocking drug.¹⁷ It has been shown in rabbit liver slices that this drug is capable of blocking the glycogenolytic effect of Adrenalin but not of glucagon.

After Staub and co-workers³ succeeded in purifying and crystallizing glucagon in 1953, experimental work in the human being became possible. The drug has been nontoxic in our hands, except when given intravenously continuously over a period of four hours at a 20 μ g per kilogram per hour dosage. Nausea and vomiting without hypoglycemia occurred in three patients so treated. Itching was noted at the site of injection in two cases.

Glucagon consistently produced hyperglycemia in our series of normal control subjects. The intravenous and subcutaneous routes produced predict-

able results. The intramuscular route was not investigated; however, Kirtley⁶ has used this route of administration and found it satisfactory in adults.

Utilizing in vitro studies with liver slices, Sutherland⁶ tested Adrenalin and glucagon together, in supramaximal amounts, and was unable to demonstrate more hyperglycemia than with either substance alone. Our in vivo studies clearly showed an additive effect. Blood sugar levels following Adrenalin plus glucagon showed twice

to a variety of factors. Cellular damage and poor nutrition with consequent inadequate supplies of liver glycogen and poor intracellular metabolism probably offer a reasonable explanation. It is unlikely that a specific deficiency of the enzyme phosphorylase plays a role here; however, our data offer no proof of this.

Glucagon definitely acts as an insulin antagonist. Our data show that insulin inactivation did not occur under the experimental conditions used.

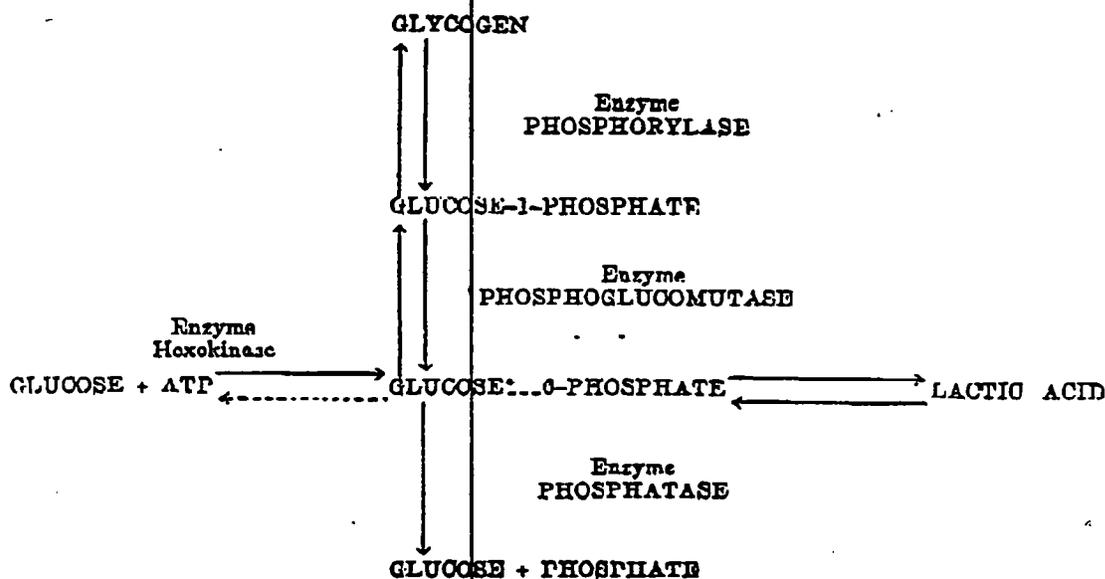


Fig. 4.—Scheme of glucose metabolism, illustrating how glycogenolysis occurs when glucagon stimulates phosphorylase activity, as shown by C. F. Cori. (The enzymatic synthesis and molecular configuration of glycogen. Carbohydrate Metabolism, The Johns Hopkins Press 1: 3, 1934.)

the increase obtained with either alone. Saturation of the enzyme system with Adrenalin or glucagon can be attained in a controlled "in vitro" technique, using supramaximal amounts. This, of course, cannot be done in the human being because of the well-known physiological effects of Adrenalin.

On the basis of theoretical considerations and the work of Kibler and associates¹² the subnormal response to glucagon of patients with extensive liver disease was expected. This may be due

With simultaneous administration of glucagon and insulin, initial hyperglycemia was followed by rapid decrease in blood sugar at the sixty-minute interval, to concentrations comparable with those resulting from insulin injection alone. The antagonism can only result, therefore, from rapid liver glycogenolysis by glucagon. Similarly, it is apparent that the drug is effective only if liver glycogen stores are adequate. In these studies, it was noted that repeated tests in the same

patients on successive days resulted in a decrease of the hyperglycemic effect of glucagon presumably due to depletion of liver glycogen. For this reason two to three days should be allowed between tests.

McQuarrie¹⁸ has demonstrated the absence of pancreatic alpha cells in some patients with idiopathic hypoglycemia and postulated a resulting deficiency of the hyperglycemic factor. In view of this, it had been hoped that glucagon would be of therapeutic value in this disease; however, the present form is too short-acting. No cumulative effect was evident with intermittent injections every three or four hours. Continuous intravenous injections failed to maintain initial blood sugar elevation.

During acute hypoglycemic episodes, symptoms could be relieved by glucagon, and blood sugar demonstrated. This shows the availability of normal liver glycogen and the lack of a normal glycogenolytic mechanism in this disease.

Glycogen storage disease may be due to specific abnormalities in the structure of glycogen or to an enzyme deficiency.⁹ In 1929, Schoenheimer¹⁹ studied the glycogen isolated from von Gierke's original case and showed it to be normal in structure. Cori and associates⁷ reported two cases with abnormal glycogen. In one, the outer chains of the glucose residues of the glycogen were very short, and in the other, they were abnormally long. In two of their cases which terminated fatally, they were able to demonstrate a specific lack of activity of glucose-6-phosphatase. In two other cases of von Gierke's disease with mild symptoms, the activity of this enzyme was diminished, whereas the enzyme was present in normal amount in two

others.⁷ In 1954, Schulman and Saturen²⁰ and Cori and Schulman²¹ again confirmed the fact that glucose-6-phosphatase is diminished in liver tissue obtained from patients with this disease. Schulman and Saturen²⁰ also suggested that the glucagon tolerance test might be of real diagnostic value in glycogen storage disease; however, our data do not substantiate this. Cases 1, 4, and 5 showed a substantial blood sugar elevation after glucagon administration. Cases 1 and 4 showed a low Adrenalin tolerance test, but a moderate hyperglycemic response to glucagon, whereas Case 6 showed abnormal hyperglycemic response to Adrenalin but none to glucagon. Case 5 revealed a normal response to both. It would appear from these data that neither the Adrenalin nor the glucagon tolerance tests are of pathognomonic value in the diagnosis of glycogen storage disease.

SUMMARY

1. Glucagon was administered to thirty-four children varying from 2 months to 13 years of age. It consistently produced a hyperglycemic effect in normal subjects. The drug was effective intravenously and subcutaneously. Dosage over 20 μ g per kilogram did not increase the hyperglycemic response.

2. The hyperglycemic effect of glucagon was increased and prolonged by simultaneous Adrenalin administration.

3. Glucagon can mobilize liver glycogen in spite of simultaneous insulin administration and is of value in controlling convulsions due to hypoglycemia.

4. Five patients with severe liver disease failed to show the normal hyperglycemic response following glu-

agon administration. Three children with glycogen storage disease showed a similar lack of hyperglycemic response but three other cases revealed moderate increases.

5. Four patients with spontaneous hypoglycemia responded to glucagon with normal hyperglycemia.

6. A low glucagon or Adrenalin tolerance test is helpful in establishing the diagnosis of glycogen storage disease, but a normal response to either test does not rule out the diagnosis.

We are appreciative of the valuable cases of glycogen storage disease placed at our disposal by the physicians mentioned.

We also wish to thank Mildred Quiroz and Marion Worthy for their able technical assistance.

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Treatment of Insulin Hypoglycemia in Diabetic Campers

A Comparison of Glucagon (1 and 2 mg.) and Glucose

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SUMMARY

The change in concentration of blood glucose in hypoglycemic diabetic boys and girls after treatment with glucagon (1 or 2 mg. given subcutaneously) or glucose (20 gm. orally) was determined. Following glucagon, at both dose levels, the concentration of blood glucose was increased after five minutes, was within the physiologic range by fifteen minutes and did not return to hypoglycemic levels during one hour. Symptoms of hypoglycemia were relieved in ten minutes in each instance. The time course of change in the concentration of blood glucose was identical at both dose levels of glucagon. With glucose orally a similar response was noted during the first fifteen minutes but the concentration of blood glucose was lower at thirty and at sixty minutes. It is concluded that the hyperglycemic response to glucagon in hypoglycemic diabetic boys and girls was identical with a 1 or 2 mg. dose.

The prompt and predictable increase in the concentration of blood glucose following glucagon administration to hypoglycemic subjects has been well documented. This response to glucagon has been observed in normal individuals,^{1,2} in patients with mental disease treated with large doses of insulin to induce coma,^{3,4} and in patients with diabetes mellitus during spontaneous,^{5,6} and insulin-induced,⁷ hypoglycemia.

Doses from 0.33 mg. to 2.0 mg. have been successfully used to reverse hypoglycemia in children and in adults. Schulman and Greben⁸ showed that the hyperglycemic effect of glucagon in schizophrenic patients made comatose by large doses of insulin was related to the dose of glucagon, being maximal with 0.2 mg. per kg. Evidence relating response to dose is less clear in the case of the hypoglycemic diabetic treated with glucagon. Eli Lilly and Company recommends a dose of 1 mg. However, several authors⁹⁻¹¹ have suggested, without

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supporting evidence, that hypoglycemia in the diabetic be treated with a 2 mg. dose. Previous studies at this camp indicated a prompt response to this dose.¹² Because of the importance of a prompt reversal of hypoglycemia, and the known safety of glucagon, it seemed desirable to determine whether the response to 1 and/or 2 mg. of glucagon differed. The purpose of this study was to determine the time course of change in concentration of blood glucose of hypoglycemic diabetic boys and girls treated with (A) 1.0 mg. of glucagon, (B) 2.0 mg. of glucagon, and (C) 20 gm. of glucose.

METHODS AND MATERIALS

Subjects were diabetics whose disorder varied from one to eleven years in duration attending Camp Immokalee, Florida's Summer Camp for Diabetic Boys and Girls. Those suspected of being hypoglycemic were brought to an infirmary; the concentration of blood glucose was estimated by a rapid screening method.¹³ Campers with a concentration of blood glucose of less than 50 mg. per 100 ml. were treated in rotation by Method A (1.0 mg. glucagon), B (2.0 mg. glucagon), or C (20 gm. of glucose given orally as 40 ml. of a 50 per cent solution containing lemon flavoring).¹⁴ If a hypoglycemic camper had been treated previously he was purposely given another form of treatment. Glucagon at both dose levels was given as a 0.5 ml. subcutaneous injection. Venous blood samples were taken before and 5, 15, 30 and 60 min. after treatment. Glucose was determined on 0.1 ml. of venous blood by the method of Dubowski.¹⁵

RESULTS

In each instance, an appreciable increase in the concentration of blood glucose was evident within five minutes; by fifteen minutes the glucose concentration

¹³Glucopon, Worthington Biochemical Corporation, Freehold, New Jersey.

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TABLE 1
Effect of glucagon and glucose on concentration of blood glucose during insulin hypoglycemia in diabetic boys and girls*

Treatment	CAMPYR No.	AGE YRS	Sex	Weight kg.	Duration of Diabetes	Insulin* before		Time of hypoglycemia	Concentration of blood glucose, mg. per 100 ml. (minutes after treatment)					
						Breakfast	Supper		0	5	15	30	60	
A. Glucagon 1 mg.	13	14	M	46	2	60 L	15 U.	1800	30	67	136	180	237	
	15	11	M	44	4	16 L	4 L	1745	45	50	91	125	77	
	26	14	M	44	11	80 L	20 R	1200	31	38	69	96	109	
	21	10	M	36	6	38 L	0	1250	35	78	114	127	121	
	47	9	F	30	1	10 L	0	1220	45	50	69	91	114	
	34	14	F	52	2	38 NPH	0	1152	63	63	91	145	181	
	43	9	F	35	6	14 L	0	1214	36	46	91	112	101	
						12 UL								
						12 K								
	40	13	F	51	2	42 L	0	1615	48	117	90	114	156	
						4 R								
	56	13	F	50	6	6 III.								
	26	14	M	44	11	26 L	0	0725	50	92	96	122	176	
						80 L	20 R	1745	35	56	99	169	164	
						80 R								
B. Glucagon 2 mg.	50	13	F	51	7	44 NPH	6 NPH	1115	30	67	74	112	114	
						8 R								
	26	14	M	44	11	80 R	20 K	1805	48	62	123	170	225	
						80 L								
	31	15	M	50	3	38 L	0	1158	39	58	75	103	96	
						12 UL								
	33	14	M	46	2	60 L	15 L	1220	35	60	128	147	181	
	28	10	M	43	4	32 NPH	0	1230	35	40	77	101	75	
	9	12	M	36	1	16 NPH	0	1050	51	80	98	98	94	
	63	12	F	34	7	28 NPH	0	1225	46	67	86	114	127	
						6 R								
	21	10	M	36	6	38 L	0	1535	45	70	78	131	153	
34	14	F	52	2	44 NPH	0	1023	20	38	66	111	123		
45	9	F	30	7	60 L	0	1735	35	38	68	144	138		
C. Glucose 20 mg.	50	13	F	51	2	44 NPH	6 NPH	0950	48	58	107	134	113	
						8 R								
	29	14	M	53	7	24 NPH	18 NPH	1200	47	62	87	110	125	
						5 R								
	61	12	F	54	8	44 L	15 L	1212	47	58	101	128	104	
						14 R								
	54	14	F	52	2	40 NPH	0	1050	39	58	90	103	75	
						4 R								
	31	15	M	50	3	42 L	0	1235	39	44	69	92	44	
						14 UL								
	21	10	M	36	6	38 L	0	1800	40	50	97	132	169	
	26	14	M	44	11	80 L	20 R	1200	55	77	115	92	34	
					80 K									
47	9	F	30	1	10 L	0	1224	54	71	107	114	65		
33	14	M	46	2	60 L	0	2030	54	63	84	69	—		
					8 UL									
61	12	F	54	9	40 L	0	1045	19	35	47	97	123		
					10 R									
					12 UL									

*Certain clinical features, the insulin dosage, the hour of hypoglycemia and the concentration of blood glucose after treatment are shown. Insulin is designated: L = Lente, R = Crystalline, NPH = Isophane and UL = Ultralente.

was within the physiologic range (table 1). More variation was noted during the second thirty minutes. Symptoms of hypoglycemia, in each instance, were less after five minutes and were relieved within ten minutes with each type of treatment. The mean concentrations

of blood glucose during the sixty minutes studied were identical after 1 and 2 mg. of glucagon; the mean concentration of glucose in those campers given 20 gm. of glucose was less at 30 ($p < 0.2$) and at 60 ($p < 0.001$) min. than that observed with glucagon (table 2, figure-

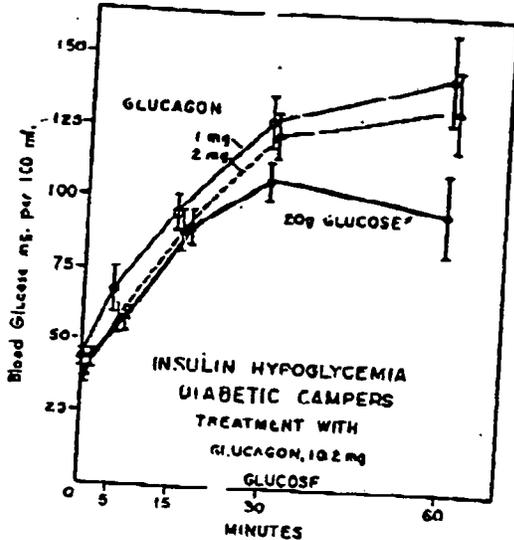
J. C. SHIPP, M.D., H. A. DELCHER, B.S., AND J. F. MUNDE, M.D.

TABLE 2

Concentration of blood glucose after treatment of insulin hypoglycemia in diabetic boys and girls*

Treatment	Concentration of blood glucose (mg. per 100 ml.)				
	Time after treatment (minutes)				
	0	5	15	30	60
A. Glucagon, 1 mg.	44 ± 3	64 ± 8	95 ± 6	128 ± 9	144 ± 15
B. Glucagon, 2 mg.	38 ± 3	58 ± 5	89 ± 7	123 ± 8	133 ± 14
C. Glucose, 20 gm. Orally	44 ± 3	58 ± 4	90 ± 6	107 ± 7	97 ± 14

*The mean concentration of blood glucose, and Standard Error of diabetic campers of table 1 are shown.

FIG. 1 The concentration of blood glucose (mean \pm S. E.) after treatment of insulin hypoglycemia with glucagon (1 and 2 mg.) and glucose.

1). Among hypoglycemic campers who received glucagon, the mean concentration of blood glucose was greater than 100 mg. per 100 ml. after sixty minutes, at sixty minutes one camper who received 1 mg. of glucagon and three who received 2 mg. of glucagon had a concentration of blood glucose of less than 100 mg. per 100 ml. In those given 20 gm. of glucose, four of nine had a blood glucose concentration of less than 100 mg. per 100 ml. at sixty minutes. In the glucose treated group, six of nine had a lower concentration of blood glucose at sixty than at thirty minutes; two (No. 26, No. 31) were hypoglycemic at sixty minutes.

NOVEMBER-DECEMBER, 1964

DISCUSSION

It is realized that the time of day with respect to the peak action of the injected insulin, the magnitude of counter-regulatory responses to hypoglycemia, and other factors, may have influenced the response to treatment. The number in each group tended to balance out factors not directly related to treatment. Five campers (Nos. 33, 26, 50, 54 and 21) were treated by all three methods. Camper 26, who received 180 U. of insulin daily, was treated by all three methods, and he received one milligram of glucagon on two occasions. The period up to fifteen or thirty minutes after treatment represented the time during which the concentration of blood glucose was most directly influenced by the treatment.

The response to each of the three forms of treatment appeared to be the same regardless of the hour at which the hypoglycemia occurred, the amount of insulin received, the age of the camper and the duration of diabetes. Others^{2,9} have suggested that the change in concentration of blood glucose after glucose was not related to the degree of hypoglycemia or the previous insulin dosage. The hyperglycemic response with one and two mg. of glucagon was not related to the weight of the patient; the dose of glucagon used was from approximately 0.02 to 0.06 mg./kg. Thus, in this study, the hyperglycemic effect was obtained with approximately one tenth the dose used by Schulman and Greben.⁹ This difference may be explained by the fact that their patients were deeply comatose after receiving large doses of insulin; furthermore, in Schulman's study even a dose of 0.2 mg./kg. did not produce normoglycemia.

These results indicate the consistent and predictable hyperglycemic effect of glucagon. The consistency of response during the first thirty minutes confirms that glucagon was promptly absorbed from the subcutaneous site and had an immediate hyperglycemic action. No camper failed to respond and there were no adverse reactions to glucagon.

Elnick and co-workers⁹ suggested that glucagon has advantages over glucose for the treatment of hypoglycemia in the patient with diabetes mellitus. Glucagon treatment utilizes endogenous glucose and the hyperglycemia produced is more predictable and rarely as excessive as may occur with a large intake of glucose. An unexpected finding in this study was the failure of 20 gm. of glucose, an amount greater than is usually recommended for symptoms of hypoglycemia,²⁴ to maintain normoglycemia for sixty minutes. The most significant advantage of glucagon is for the treatment of the unconscious or uncooperative hypoglycemic patient. In a

TREATMENT OF INSULIN HYPOGLYCEMIA IN DIABETIC CAMPERS

camp for diabetic boys and girls its use for hypoglycemia prevents feigned reactions^{11,12} and provides a practical means of acquainting the young diabetics with glucagon.

SUMMARIO IN INTERLINGUA

Tractamento de Hypoglycemia Insulinogene in Juvenes Diabeticos Surrmanas in un Campo de Vacantia

La alteration del concentration de glucosa del sanguine post tractamento con glucagon in administrationes subcutanee de 1 o 2 mg o con glucosa in administrationes oral de 20 mg esseva determinate in pueros e pueros diabetic in statu de hypoglycemia. Post glucagon, a ambe nivellos de dosage, le concentration sanguinee de glucosa esseva augmentate intra cinque minutos; illu attingeva valores physiologic intra dece-cinque minutos; e illo non retornava a nivellos hypoglycemic durante un hora. Le symptomas de hypoglycemia esseva alleviate in omne caso intra dece minutos. Le curso temporal del alteration in le concentration sanguinee de glucosa esseva identic a ambe nivellos de glucagon. Con glucosa in administration oral, un simile responsa esseva notate durante le prime dece-cinque minutos, sed le concentration de glucosa sanguinee esseva plus basse post trenta e post sexanta minutos. Es concludite que le responsa anti-hypoglycemic a glucagon in hypoglycemic pueros e pueros diabetic esseva identic in le caso de un dose de 1 mg e in le caso de un dose de 2 mg.

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Hypoglycaemia in Childhood Diabetes

BEST-POSSIBLE

II. Effect of Subcutaneous or Intramuscular Injection of Different Doses of Glucagon

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ABSTRACT. Åman, J. and Wranné, L. (Department of Paediatrics, Örebro Medical Centre Hospital, Örebro, Sweden). Hypoglycaemia in childhood diabetes. II. Effect of subcutaneous or intramuscular injection of different doses of glucagon. *Acta Paediatr Scand* 77: 548, 1988.

Hypoglycaemia (blood glucose 1.3–2.5 mmol/l) was induced in thirty diabetic children by reduction of their morning meal. Glucagon, 10 or 20 µg/kg was then given by intramuscular or subcutaneous injection. Ten min later, all signs of hypoglycaemia had disappeared and blood glucose concentrations increased by 0.7–3.3 mmol/l. Glucagon plasma concentrations at glucose nadir were low, 23 ± 8 pmol/l, rose to 300 ± 42 ten min after the injection and reached peak values after another ten min. Later, a slow decrease was noted. No significant difference of blood glucose or plasma glucagon concentrations were found after subcutaneous or intramuscular injections of 20 µg/kg. After 10 µg/kg, slightly lower increase of blood glucose was seen, but the clinical effect was equally good. Nausea occurred in four children given 20 µg/kg. The rise of blood glucose did not correlate to the peak glucagon concentration obtained after the injection but showed significant correlations to the lowest glucose concentration and, inversely, to the concentration of free insulin in blood at glucose nadir. It is concluded that glucagon injections are effective in hypoglycaemia in insulin-treated diabetic children and that the injection of 10–20 µg/kg gives long-standing supraphysiological concentrations which make repeated injections unnecessary. *Key words: childhood diabetes, hypoglycaemia, glucagon treatment.*

Hypoglycaemia is a frequent complication in the treatment of insulin-dependent diabetes mellitus (1, 2). While hypoglycaemia in the conscious diabetic can be treated by oral glucose, problems arise in its severe forms when the patient is unable to swallow. Buccal and rectal administration of glucose are useless (3, 4). In the hospital glucose is easily given intravenously, but not at home. Glucagon, administered by parents or other adults, remains the method of choice for the unconscious patient outside hospital.

However, studies of the effect of glucagon have given conflicting results. Some studies showed a fast increase of blood glucose and relief of symptoms (5–7) but another found glucagon effective only in 40% of the patients (8). All these studies concerned adults. In a study of non-diabetic children, the optimum dose was considered to be 20 µg/kg (9). The effect in diabetic children does not seem to have been investigated. Whether subcutaneous or intramuscular injection gives the best response is also a matter of dispute; some studies claim good effect by the subcutaneous route (5, 6) while others do not (7). Side effects of glucagon treatment of hypoglycaemia have not been discussed.

In the present study, the effects of glucagon injections on clinical signs, blood glucose and plasma glucagon concentrations in hypoglycaemic diabetic children are reported. The effects of giving glucagon by intramuscular and subcutaneous injections are compared, as are the effects of giving 20 and 10 µg glucagon/kg bodyweight. Finally, an attempt is made to explain the variations of the blood glucose response to glucagon.

PATIENTS AND METHODS

The study group comprised thirty diabetic children. Clinical data are given in Table 1. Hypoglycaemia was induced as described earlier (4, 10). When hypoglycaemic symptoms were obvious, blood samples

were obtained followed by the injection of glucagon. This moment was designated "glucose nadir". In the first randomized series of ten children, 20 µg/kg was injected intramuscularly or subcutaneously. In the second series of subcutaneous injections, another five children were given 20 µg glucagon/kg body-weight and fifteen children were given 10 µg/kg. All injections were given by one of the authors (J. Å.) using 30 mm injection cannulae. Intramuscular injections were given perpendicular to the skin surface and subcutaneous injections at a 45 degree angle. No child had much subcutaneous fat and the depth of injection was further controlled by giving the intramuscular injections through flattened and stretched skin and the subcutaneous injection in a lifted skinfold. After the glucagon injection, blood glucose concentrations were measured at frequent intervals (Table 2). A total of seven signs of hypoglycaemia were noted at glucose nadir and 10 min later as described earlier (10).

Glucagon, adrenalin, cortisol and free insulin concentrations were measured at glucose nadir (Table 1). Additional studies of glucagon concentrations were made during the following 60 min in the first series and 30 min in the second series (Table 3). No food was given during this time. Methods of hormone analysis are described separately (10). Student's *t*-tests for unpaired data and linear regression analysis were used. Data are shown as mean ± SD. The study was approved by the local committee of medical ethics.

RESULTS

At glucose nadir, all children had hypoglycaemic signs and the blood glucose concentration was 1.3–2.5 mmol/l. Signs and glucose concentrations were similar in the two series. Within 10 min after the injection of glucagon, glucose concentration had increased by 0.7–3.3 mmol/l (Table 2). At that time, all hypoglycaemic signs had disappeared. Blood glucose con-

Table 1. Clinical data of the study groups (mean ± SD)

Injected glucagon		Pat. no.	Sex (F/M)	Age (yrs)	Diabetes duration (yrs)	C-peptide <0.1 nmol/l >0.1 nmol/l (no.)	Levels at glucose nadir of			
µg/kg	im/sc						Free-insulin (mU/l)	Glucagon (pmol/l)	Adrenalin (nmol/l)	Cortisol (nmol/l)
<i>First series</i>										
20	im	5	3/2	12.2±3.0	5.4±3.0	5/0	45±27	18±9	1.8±0.8	606±123
20	sc	5	1/4	11.8±3.2	3.2±1.3	4/1	51±17	19±7	2.7±1.4	549±95
<i>Second series</i>										
20	im+sc	15*	5/10	11.4±2.5	3.1±2.8	9/6	51±20	22±8	2.3±1.3	571±104
10	sc	15	3/12	12.8±2.6	2.7±3.6	5/10	61±17	24±9	3.3±2.5	578±112

* Including the 10 children of the first series.

Table 2. Effect of injected glucagon on the blood glucose concentration (mean ± SD)

Injected glucagon		Blood glucose before injection (mmol/l)	Δ-Blood glucose after glucagon injection, mmol/l						
µg/kg	im/sc		5 min	10 min	20 min	30 min	40 min	50 min	60 min
<i>First series</i>									
20	im	1.9±0.3	1.0±0.6	2.0±0.9	3.7±1.6	4.2±2.0	4.4±2.2	4.6±2.5	4.8±2.9
20	sc	1.7±0.3	0.5±0.4	1.7±0.7	3.0±1.2	3.4±1.6	3.8±1.3	3.7±1.2	3.1±1.0
<i>Second series</i>									
20	im+sc	1.8±0.3	0.7±0.5	1.7±0.7	3.0±1.2	3.5±1.5	-	-	-
10	sc	1.8±0.4	0.4±0.2	1.1±0.3	2.4±1.1	2.9±1.6	-	-	-

* *p*<0.05; ** *p*<0.01.

tinued to rise in most children, but to a varying degree (Table 2). In no child did the blood glucose level return to its previous nadir (Table 2).

Injection technique. All hypoglycaemic signs were rapidly relieved whether glucagon had been given subcutaneously or intramuscularly. Ten min after the injection, the mean glucose increase and the mean glucagon concentration were slightly but insignificantly higher after the intramuscular injection. Peak concentrations of glucagon were seen after 20 min and did not return to the pre-injection levels during the 30 or 60 min of observation.

Dose injected. Since the effects of subcutaneous and intramuscular injections of 20 µg/kg appeared similar, these two groups were combined and another group of five children added. In order to test a lower dose of glucagon, we gave fifteen children 10 µg/kg. Although the effect on clinical signs was equally good in all children, the increase of blood glucose concentration after 10 min was less in those given 10 µg/kg, 1.1 ± 0.3 mmol/l, as compared to 1.7 ± 0.7 in those given 20 µg/kg ($p < 0.01$). After 20 and 30 min, a non-significant difference was seen (Table 2). Also, as could be expected, the concentration of glucagon was lower in those given 10 µg/kg, but not to a significant degree until 20 min after the injection ($p < 0.01$, Table 3).

The influence of other parameters. After 20 µg glucagon/kg a significant, direct correlation was found between the increase of blood glucose at 10 min and the blood glucose concentration at nadir ($r = +0.65$; $p < 0.01$) and an inverse correlation to the free insulin concentration at nadir ($r = -0.75$; $p < 0.01$). After 10 µg/kg the free insulin but not the glucose concentration at nadir showed a similar significant correlation to the rise of blood glucose. No correlations were found between the rise of blood glucose and cortisol or adrenalin concentrations at glucose nadir or glucagon concentrations 10 min after injection (Fig. 1).

Side effects. One to three hours after the glucagon injection, after being offered food and drink, four children felt nauseous and one of them vomited. All these children were given 20 µg/kg. The youngest children, 7–10 years old, were all nauseous. The peak glucagon concentration found in these children was 593 ± 189 pmol/l, as compared to 410 ± 162 pmol in those who received 20 µg/kg but were unaffected. However, the difference between the groups was not significant. Among those given 10 µg/kg, none felt nauseous. The peak glucagon concentration in these children was 300 ± 140 pmol/l.

DISCUSSION

In this study, hypoglycaemic signs were equally effectively relieved by intramuscular and subcutaneous injections of 10 or 20 µg glucagon per kg bodyweight. Although on the average, the blood glucose concentrations rose more slowly after the injection of 10 µg/kg as com-

Table 3. Plasma concentrations of glucagon, mean \pm SD, before and after intramuscular or subcutaneous injections of 10 or 20 µg glucagon/kg

Injected glucagon		Plasma glucagon before injection (pmol/l)	Plasma glucagon after glucagon injection, pmol/l				
µg/kg	im/sc		10 min	20 min	30 min	45 min	60 min
<i>First series</i>							
20	im	18 \pm 9	320 \pm 146	450 \pm 253	414 \pm 253	296 \pm 132	197 \pm 84
20	sc	19 \pm 7	282 \pm 139	464 \pm 214	418 \pm 88	326 \pm 90	275 \pm 50
<i>Second series</i>							
20	im+sc	22 \pm 8	331 \pm 125	481 \pm 186	427 \pm 149	-	-
				..	***		
10	sc	24 \pm 9	263 \pm 116	300 \pm 140	226 \pm 79	-	-

** $p < 0.01$; *** $p < 0.001$.

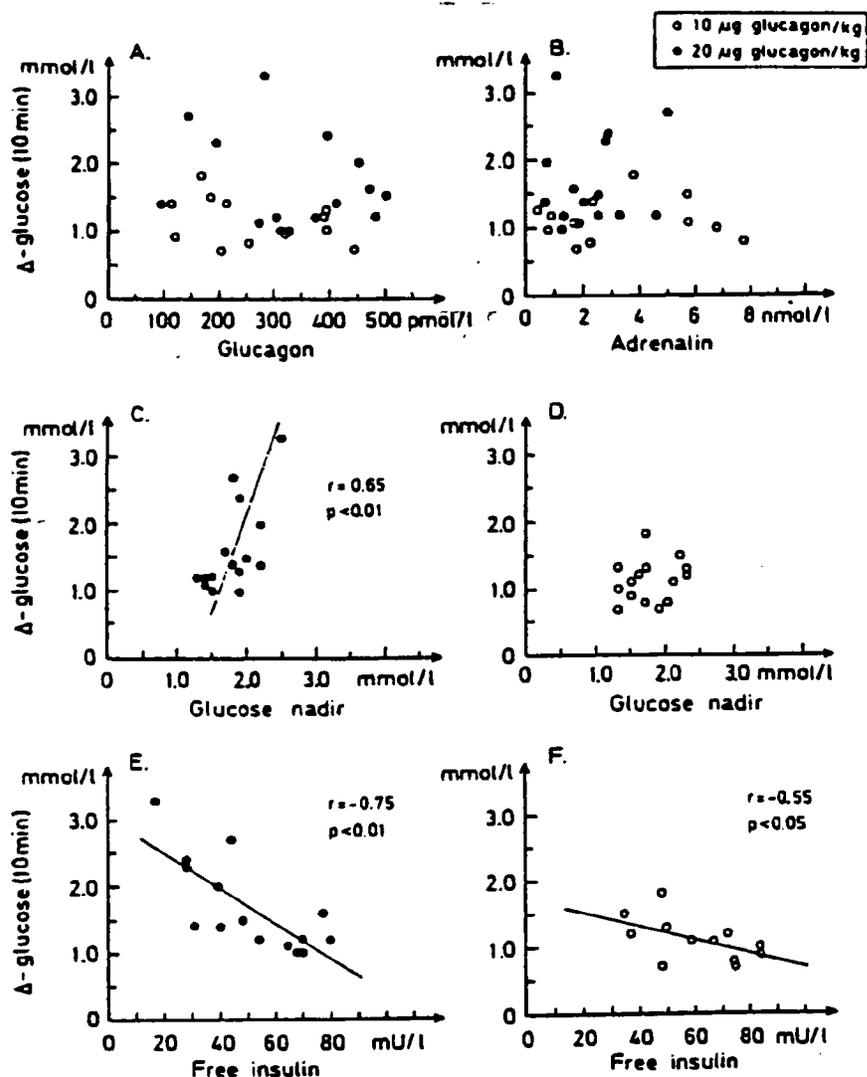


Fig. 1. Rise of blood glucose concentration 10 min after injection of glucagon compared to (A) Glucagon concentration 10 min after injection, (B) adrenalin concentration at glucose nadir, (C) glucose concentration at nadir (20 μ g glucagon/kg), (D) glucose concentration at nadir (10 μ g glucagon/kg), (E) free insulin concentration at glucose nadir (20 μ g glucagon/kg) and (F) free insulin concentration at glucose nadir (10 μ g glucagon/kg).

pared to 20 μ g/kg, this did not seem to be clinically important. Our findings are supported by a recent study of healthy adults in which no difference was found between the effects of subcutaneous and intramuscular injections of glucagon (11).

The amounts of glucagon injected gave plasma concentrations higher than those seen in venous (12) or portal blood (13) of healthy adults during insulin-induced hypoglycaemia. In peripheral plasma of these adults, the mean concentrations of glucagon rose from 15 to 50 pmol/l (12). Portal blood contained on the average 70% higher concentrations (13). Compared to the concentrations found in those studies, we found that therapeutic glucagon injections gave much higher levels, probably higher than necessary for maximum effect. This assumption is supported by the lack of correlation between the glucagon concentration at 10 min and the rise of blood glucose (Fig. 1).

We have shown that the endogenous glucagon response to hypoglycaemia is blunted in diabetic children (10) and similar findings have been reported from studies of adult diabetics (12, 14, 15). These findings add to the conclusion that glucagon injection is the method of choice for relieving hypoglycaemia in the unconscious child when intravenous injection of glucose is not possible.

It is recommended by some manufacturers that the glucagon injection should be repeated if the desired effect has not been obtained in 10–15 min. The present findings of sustained high plasma concentrations of glucagon contradict this assertion. The lack of effect must de-

pend on causes other than insufficient concentrations of circulating glucagon, and therefore the injection should not be repeated at short intervals. We found that the increased blood glucose concentrations were sustained for at least 30 min. Thus there is no great hurry to give the children food or drink after the glucagon injection.

The rise of blood glucose during the first 10 min correlated inversely to the plasma concentration of free insulin at glucose nadir (Fig. 1). This indicates that the hepatic glucose production induced by glucagon is counteracted by insulin which also stimulates peripheral glucose utilization (16).

Glucagon stimulates glycogenolysis (17, 18). Consequently, depleted glycogen liver stores should reduce the effect of glucagon injections. In this study, glycogen was probably available in the liver. Therefore, our study does not allow conclusions concerning the effects of glucagon on hypoglycaemia elicited by heavy physical exercise or prolonged starvation. Further studies are necessary before we can recommend glucagon in these situations.

A placebo effect of the injection on blood glucose concentration seems unlikely. An earlier study of rectal glucose infusion did not lead to any rise in blood glucose despite high expectations of a positive effect by parents and children (4). Therefore, the inclusion of a placebo group was considered unnecessary.

CONCLUSIONS

We have found that the injection of glucagon is an efficient method of relieving hypoglycaemia in the hypoglycaemic child. The effect seems to be equally good, whether glucagon is given subcutaneously or intramuscularly. This is advantageous, since hypoglycaemia can be accompanied by seizures or muscular twitchings, which make the exact injection depth difficult to ascertain. The injection of 10 $\mu\text{g}/\text{kg}$ was equally effective in relieving hypoglycaemic signs as was the injection of 20 $\mu\text{g}/\text{kg}$ but the latter dose gave a stronger glucose response. However, the finding of higher glucagon concentrations among those children who became nauseous makes it probable that the lower dose should be preferred, at least in young children. Once injected, the glucagon dose should not be repeated. It is not necessary to give food during the first 30 min after the injection, since blood glucose and glucagon concentrations are elevated for at least 30 min.

ACKNOWLEDGEMENT

The study was supported by Novo industri, Bagsværd, Denmark.

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NDA Amendment

May 22, 1998

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**Re: NDA 20-918 GlucaGen® [glucagon (rDNA)]
NDA Amendment
Response to CMC Review Comment
Patent Information**

ORIG ALB...
BC

Dear Dr. Sobel,

We refer to NDA 20-918 GlucaGen® [glucagon (rDNA)].

We are enclosing in duplicate, the 12 months interim stability report for GlucaGen® (development item #5-1972-05; production no. for US item 5-9400-44) and the supportive 24 month interim stability report. (b)(4)

(b)(4)

Additionally, we are submitting a separate patent information statement indicating no relevant patents. The patent certification in the original NDA indicated the same.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

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Barry Reit, Ph. D.
Vice President, Regulatory Affairs

/mk

Enclosures

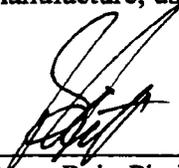
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Patent Information

No relevant patents: In accordance with 314.53 (c)(3) Novo Nordisk declares that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by Novo Nordisk engaged in the manufacture, use or sale of the drug product.



Barry Reit, Ph. D.
Vice President, Regulatory

5/22/98
Date

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DATE

May 22, 1998

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EXCLUSIVITY SUMMARY for NDA # 20-918 SUPPL # _____

Trade Name Glucagen Generic Name Glucagon for injection
Applicant Name Novo Nordisk HFD-510 (XDNA)

Approval Date _____

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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 / NO /

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b) Is it an effectiveness supplement?

YES / NO /

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 /

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:

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d) Did the applicant request exclusivity?

YES / / NO / /

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

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 / / NO / /

(Jilly) If yes, NDA # 12-122 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).

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

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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 # _____

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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 # _____

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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.

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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.

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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 / /

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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:**

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- (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: _____

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- (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: _____

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- (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 # _____

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Investigation #3, Study # _____

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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.

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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 # _____

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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 # _____

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- 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 # _____

APPEARS THIS WAY ON ORIGINAL

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

APPEARS THIS WAY ON ORIGINAL

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 _____

APPEARS THIS WAY ON ORIGINAL

Investigation #2

APPEARS THIS WAY ON ORIGINAL

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: _____

APPEARS THIS WAY ON ORIGINAL

/s/ _____

Signature _____ Date 6-17-98
Title: Project Manager

/s/ _____

Signature of Division Director _____ Date 6/22/98

APPEARS THIS WAY ON ORIGINAL

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

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Debarment Statement

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, Novo Nordisk Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Barry Reit, PhD
Vice President
Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

Group Leader's Note

NDA 20-918
GlucaGen
glucagon

June 19, 1998

~~APPEARS THIS WAY ON ORIGINAL~~

The effect of this NDA is to provide for the first time a glucagon drug product that is entirely (b)(4) No clinical studies are needed to demonstrate safety and effectiveness though the sponsor has submitted clinical studies and has extensive post-marketing experience from use of this product licensed in Europe. Technical problems with the (b)(4) used for the original pK comparison of Glucagen and Lilly's marketed (b)(4) product have been well discussed by Dr. Misbin. In the most recent pK study, measured plasma glucagon levels were lower than would be expected. This appears again to be a technical problem. Given the large dose excess for reversing hypoglycemia present in the recommended unit dose, this does not represent a significant clinical issue. Nor is there a substitutability issue and consequent need to show bioequivalence with the currently available (b)(4) product.

~~APPEARS THIS WAY ON ORIGINAL~~

Recommendation: The NDA should be approved with the revised labeling recommended by the Division.

/s/

Alexander Fleming, M.D.

~~APPEARS THIS WAY ON ORIGINAL~~

cc:
HFD-510
/NDA
/div. file
/R. Misbin

~~APPEARS THIS WAY ON ORIGINAL~~

Safety Update

June 17, 1998

Solomon Sobel, M.D.
Director, Division of Metabolism & Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 20-918
GlucaGen® [glucagon (rDNA)]

Dear Dr. Sobel:

APPEARS THIS WAY ON ORIGINAL

Reference is made to NDA 20-918 GlucaGen® [glucagon (rDNA)]. As requested by Julie Rhee during her telephone conversation with Mary Ann McElligott, Director, Regulatory Affairs, and in accordance with 21 CFR §314.50(d)(5)(vi)(b), enclosed is a Safety Update for GlucaGen® [glucagon (rDNA)]. The Safety Update is a listing of the spontaneously reported adverse events for the period January 16, 1998 through June 10, 1998. The NDA Safety Update was current from September 1, 1989 through July 31, 1997. The 120-Day Safety Update submitted January 20, 1998 was for the period August 1, 1997 through January 15, 1998. MedWatch forms are also provided for the IND Safety Reports.

APPEARS THIS WAY ON ORIGINAL

If you have any questions regarding this submission, please contact Mary Ann McElligott at the above number.

Sincerely,
NOVO NORDISK PHARMACEUTICALS INC.

M. McElligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

BR/pk
Enclosure

F:\...glucagon\safety update 6-17-98

UAT
/s/ [Redacted Signature]

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Based on the results of chemistry review #2 and consultation with the lead field investigator, the sponsor was asked to provide the following as an amendment to the NDA:

1. The sponsor was asked to clarify the sub-lot sizes for the drug substance (b)(4)
2. The sponsor was asked (b)(4)
(b)(4)
3. The sponsor was asked to replace the term (b)(4)
(b)(4)
(b)(4) The sponsor was asked not to re-submit the relevant section of the NDA with those corrections, but, rather to stipulate that the changes had been made.

/s/

Name: William K. Berlin, Review Chemist

Date: 6-10-98

NDA#: 20-918

**Telecon/Meeting
initiated by:** WKBerlin

Applicant/Sponsor

FDA

By: Telephone

Product Name:
GlucaGen

Firm Name:
Novo Nordisk

**Name and Title of Person
with whom conversation
was held:**

Mary Ann McElligot

Phone:
609-987-5831

Consult #905 (HFD-510)

~~APPEARS THIS WAY ON ORIGINAL~~

GLUCAGEN

glucagon (rDNA) injection

The Committee noted a sound-alike/look-alike conflict with the following USAN: glucagon. The committee felt there was a high potential for confusing the proprietary name of this product with the generic name, leading to an inappropriate choice of product.

Overall, the Committee finds the proposed proprietary name unacceptable.

ls/ [Redacted Signature] *2/23/98*, Chair
CDER Labeling and Nomenclature Committee

~~APPEARS THIS WAY ON ORIGINAL~~

REQUEST FOR TRADEMARK REVIEW

APPEARS THIS WAY ON ORIGINAL

To: Labeling and Nomenclature Committee
Attention: Dr. Daniel Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Metabolism and Endocrine D. P./ HFD-510
William K. Berlin 301-827-6370

Date: 10-27-97

APPEARS THIS WAY ON ORIGINAL

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: GlucaGen® **NDA #:** 20-918

Established name, including dosage form: Glucagon (rDNA) injection

APPEARS THIS WAY ON ORIGINAL

Other trademarks by the same firm for companion products: Novolin® for rhInsulin

Name and address of applicant: Novo Nordisk Pharmaceuticals, Inc.
100 Overlook Center
Princeton, NJ 08540-7610

APPEARS THIS WAY ON ORIGINAL

Indications for Use (may be a summary if proposed statement is lengthy):
hypoglycemia and diagnostic aid

APPEARS THIS WAY ON ORIGINAL

Dosage Form: sterile powder for injection/ **Strengths:** 1 mg/ **Route of Administration:** injection **Dispensed:** R

Initial comments from the submitter (concerns, observations, etc.): Tradename submitted in the NDA original submission

APPEARS THIS WAY ON ORIGINAL

NOTE: *Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.*

Rev Oct. 1993

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
June 10, 1998

Re: 6/9/98 Biopharm review

I called Dr. McElligott and mentioned that subject 10 was reported to have a pre-study serum potassium of (b)(4), a value almost incompatible with life and asked her to clarify how a healthy subject with such a potassium was enrolled in the study.

She agreed to check with the medical people and get back to me asap.

Following this t-con, Dr. McElligott faxed the attached copy of lab printout for subject 10 which shows serum potassium of (b)(4)

Attachment: 6-10-98 fax from Dr. McElligott

cc: OrigNDA
HFD-510/DivFile
HFD-870/shore

APPEARS THIS WAY ON ORIGINAL

ksl

Name: Julie Rhee

NDA#: 20-918

**Telecon/Meeting
initiated by:**

Applicant/Sponsor

FDA

By: Telephone

Product Name:
Glucagen

Firm Name:
NovoNordisk

**Name and Title of Person
with whom conversation
was held:**

Mary Ann McElligott, Ph.D.
Regulatory Affairs

Phone:
(609) 987-5831

Simonerty

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: April 21, 1998
<p>I called Dr. McElligott and conveyed the following requests from Dr. Shore:</p> <ol style="list-style-type: none">1. What is the formulation of GlucaGen used in Study 101/UK?2. Is the formulation and manufacturing process and site the same as the proposed to-be-marketed GlucaGen?3. What was the batch size of the 101/UK formulation and how does that compare with the to-be-marketed GlucaGen batch size? <p>CC:OrigNDA HFD-510/DivFile HFD-870/Shore</p> <p style="text-align: center;">APPEARS THIS WAY ON ORIGINAL</p> <p>lsl</p> <p>Name: Julie Rhee</p>	<p>NDA#: 20-918</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> Applicant/Sponsor <input checked="" type="radio"/> FDA</p> <p>By: Telephone</p> <p>Product Name: GlucaGen</p> <p>Firm Name: Novo Nordisk</p> <p>Name and Title of Person with whom conversation was held: Mary Ann McElligott, Ph.D. Regulatory Affairs</p> <p>Phone: (609) 987-5831</p>



NDA 20-918

Food and Drug Administration
Rockville MD 20857

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center
Suite 200
Princeton, New Jersey 08540-7610

MAR 20 1998

~~APPEARS THIS WAY ON ORIGINAL~~

Dear Dr. Reit:

We acknowledge receipt on March 13, 1998, of your amendment dated March 12, 1998, to your new drug application for GlucaGen® [glucagon (rDNA origin)].

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 June 23, 1998.

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

Sincerely yours,

/s/

~~APPEARS THIS WAY ON ORIGINAL~~

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~~



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rhee.3

Food and Drug Administration
Rockville MD 20857

NDA 20-918

MAR 20 1998

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center
Suite 200
Princeton, New Jersey 08540-7610

Dear Dr. Reit:

APPEARS THIS WAY ON ORIGINAL

We acknowledge receipt on March 13, 1998, of your amendment dated March 12, 1998, to your new drug application for GlucaGen® [glucagon (rDNA origin)].

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 June 23, 1998.

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

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

/s/

3/20/98

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

APPEARS THIS WAY ON ORIGINAL

cc:

Original NDA 20-918
HFD-510/Div. Files
HFD-510/J.Rhee
DISTRICT OFFICE

Drafted by: JRhee /March 19, 1998/
Initialed by: Galliers 3-20-98
final: JRhee 3-20-98

c:wpfiles/letter/20918ext.ltr

REVIEW EXTENSION

OCT 21 1997

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: October 20, 1997
<p>I called Dr. McElligott and informed her that we had the filing meeting and if they could provide the assay validation data (requested by Dr. Rob Shore of Biopharm during their 10/17/97 t-con) by 11/7/97, we will file the NDA as a Priority application.</p> <p>Dr. McElligott stated that she had received 100 pages of fax from Europe and is going to go thru them but did not think they will have any problem meeting the 11/7/97 date.</p> <p>I also asked her to look into (b)(4) assay values as requested by Dr. Misbin. She said the company is aware of the low values and is looking into them.</p> <p>cc: OrigNDA HFD-510/DivFile HFD-510/Misbin HFD-870/Shore</p> <p>(b)(4)</p> <p>(b)(4)</p> <p>Name: Julie Rhee</p>	<p>NDA#: 20-918</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> Applicant/Sponsor <input checked="" type="radio"/> FDA</p> <p>By: Telephone</p> <p>Product Name: GlucaGen</p> <p>Firm Name: Novo Nordisk</p> <p>Name and Title of Person with whom conversation was held: Mary Ann McElligott, Ph.D. Regulatory Affairs</p> <p>Phone: (609) 987-5831</p>



RHEE

NDA 20-918

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center
Suite 200
Princeton, New Jersey 08540-7610

OCT 22 1997

Dear Dr. Reit:

APPEARS THIS WAY ON ORIGINAL

Please refer to your September 18, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GlucaGen® [glucagon (rDNA)].

We also refer to our acknowledgment letter dated September 26, 1997, which stated that the drug review priority classification for this application would be standard (S).

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.

The decision on whether or not to file this application will be made by November 22, 1997, the filing date. Our initial review identified deficiencies which could prevent filing this application. Please submit your responses to the following information requests by November 7 to allow sufficient review time before the filing:

(b)(4)



NDA 20-918
Page 2

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

Sincerely yours

ksl

for 10-22-97
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

cc:

Original NDA 20-918
HFD-510/Div. Files
HFD-510/Misbin/Berlin/HRhee
HFD-870/Shore
HFD-160/Uratani

APPEARS THIS WAY ON ORIGINAL

Drafted by: jr/October 20, 1997/
Initialed by: Galliers 10-22-97
final: JRhee 10-22-97

c:wpfiles/letter/20918p.ack

ksl

10-22-97

GENERAL CORRESPONDENCE

APPEARS THIS WAY ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

RHEE

Food and Drug Administration
Rockville MD 20857

NDA 20-918

Novo Nordisk Pharmaceutical, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center, Suite 200
Princeton, New Jersey 08540-7610

SEP 26 1997

APPEARS THIS WAY ON ORIGINAL

Dear Dr. Reit:

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: GlucaGen® [glucagon (rDNA)]

Therapeutic Classification: Standard

Date of Application: September 18, 1997

Date of Receipt: September 23, 1997

APPEARS THIS WAY ON ORIGINAL

Our Reference Number: 20-918

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 November 22, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Julie Rhee, Project Manager, at (301) 443-3510.

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

Sincerely yours,

ks/

9/26/97

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

APPEARS THIS WAY ON ORIGINAL

Page 2
NDA 20-918

cc:

Original NDA 20-918
HFD-510/Div. Files
HFD-510/CSO/J.Rhee
HFD-510/Misbin/Berlin/Steigerwalt
DISTRICT OFFICE

APPEARS THIS WAY ON ORIGINAL

Drafted by: JRhee/September 25, 1997/

c:wpfiles/letter/20918ack.ltr
n:julie/letter/20918ack.ltr

Concurrence Galliers 9-26-97

Final: JRhee 9-26-97 *JS* 9-26-97

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY ON ORIGINAL

NDA Amendment

June 22, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

APPEARS THIS WAY ON ORIGINAL

Re: NDA 20-918 GlucaGen® [glucagon (rDNA origin) for injection]
NDA Amendment

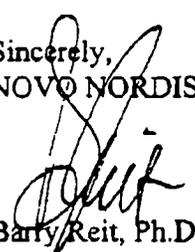
Dear Dr. Sobel, APPEARS THIS WAY ON ORIGINAL

We refer to NDA 20-918 GlucaGen® [glucagon (rDNA origin) for injection].

NDA 20-918 is submitted under section 505(b)(2). The approved drug product in the listing "Approved Drug Products" is glucagon hydrochloride injectable; injection glucagon, (animal source, pancreatic origin). The chemical structure of the glucagon in GlucaGen® [glucagon (rDNA origin) for injection] is identical to the glucagon extracted from beef and pork pancreas. The fact that this drug product is listed in the "Approved Drug Products" is the basis for the 505(b)(2) submission.

If you have any questions, please contact Mary Ann McElligott, Ph.D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.


Barry Reit, Ph.D.
Vice President, Regulatory Affairs

/mk

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

NDA Amendment

June 22, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857 **APPEARS THIS WAY ON ORIGINAL**



Novo Nordisk

**Novo Nordisk
Pharmaceuticals Inc.**

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

**Re: NDA 20-918 GlucaGen® [glucagon (rDNA origin) for injection]
NDA Amendment - Labeling**

Dear Dr. Sobel, **APPEARS THIS WAY ON ORIGINAL**

We refer to NDA 20-918 GlucaGen® [glucagon (rDNA origin) for injection].

As requested, we are enclosing the Physicians' Package Insert with the annotations removed. This package insert is the same as Novo GlucaGen® PI Revision 6 (June 18, 1998) submitted in the letter dated June 19, 1998 with the exception of the removal of the annotations. **APPEARS THIS WAY ON ORIGINAL**

The electronic copy (file name: Unannotated Package Insert) is enclosed.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

APPEARS THIS WAY ON ORIGINAL
Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.


Barry Reit, Ph. D.
Vice President, Regulatory Affairs

/mk

Enclosures

APPEARS THIS WAY ON ORIGINAL

NDA Amendment

June 16, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



**Novo Nordisk
Pharmaceuticals Inc.**

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 20-918 GlucaGen® [glucagon (rDNA)]
NDA Amendment - CMC Update



Dear Dr. Sobel,

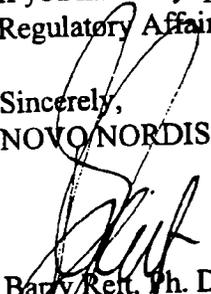
We refer to NDA 20-918 GlucaGen® [glucagon (rDNA)].

We are enclosing amendments to the NDA based on our discussions with Dr. William Berlin yesterday.

Based on the Pre-Approval Inspection of Feb. 17 - Mar. 5, 1998, we are amending several sections of the NDA to be in accordance with changes that have been made. They are linked to the PAI Observation number for ease of review. Reference is made to the original NDA for the revision.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVONORDISK PHARMACEUTICALS, INC.


Barry Reit, Ph. D.
Vice President, Regulatory Affairs

/mk

Enclosures

Desk copy - Bill Berlin
cc: Full copy to Field Office with Field Copy Certification

NDA Amendment

June 5, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7811
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-918 GlucaGen® [glucagon (rDNA)]
Response to Reviewers' Query

Dear Dr. Sobel,

APPEARS THIS WAY ON ORIGINAL

The following information is provided in response to Dr. Misbin's query of October 2, 1997 and Dr. Shore's comments during our telephone discussion on June 1, 1998 regarding plasma glucagon levels.

We are providing an explanation and have attached the literature reference discussed.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

APPEARS THIS WAY ON ORIGINAL

M. A. McElligott for Barry Reit

Barry Reit, Ph., D.
Vice President, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

June 2, 1998



Novo Nordisk

120

Dr. Robert Shore
Food and Drug Administration
CDER/ODEII/DMEDP HFD-510
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

APPEARS THIS WAY ON ORIGINAL

**Re: Responses to Comments on Preliminary Assay Validation Results
for GlucaGen® Study 007
NDA 20-918 GlucaGen® [glucagon (rDNA)]**

Dear Dr. Shore,

Attached is the response to your fax of May 28, 1998 providing your comments on the Preliminary Assay Validation data. The responses indicate where in the final validation report these issues are addressed.

APPEARS THIS WAY ON ORIGINAL

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,

Mary Ann McElligott/mke

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

Attachment

/mk

ORIG AMENDMENT

BB

NDA Amendment

May 26, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 20-918
GlucaGen® 1mg [glucagon (rDNA)]
NDA Amendment, Final Study Report GLU/USA/007/USA

Dear Dr. Sobel,

We refer to NDA 20-918 for GlucaGen® 1mg [glucagon (rDNA)].

We are submitting in duplicate, Study Report for Protocol GLU/USA/007/USA entitled "Pharmacokinetic Assessment of Glucagon after Intramuscular Injection." The assay validation for glucagon measurement is also enclosed. Responses to the Biopharm Review comments (May 8, 1998) are addressed in these reports. Two additional responses are explained below.

Blue & loads appear too low

The batch numbers were HR40162 for GlucaGen® and GR41031 for Sterile Water for Reconstitution in the study. These batches were from a full scale production size batch, made on the same equipment using the same manufacturing procedures that will be used for making the final to-be-marketed product at the proposed site of manufacture (b)(4). Additionally, male subjects were used in Study 007 which needed to be conducted expeditiously to confirm plasma concentrations after one dose of glucagon. Male volunteers fulfilled this objective and females had been studied previously in GlucaGen® Study 006.

If you have any further questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph. D.
Vice President, Regulatory Affairs

/mk
Enclosure

*Reviewing Desk
04-30-98*

APPEARS THIS WAY ON ORIGINAL

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

ORIGINAL

NDA Amendment

May 22, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 20-918 GlucaGen® [glucagon (rDNA)]
NDA Amendment
Response to CMC Review Comment
Patent Information

ORIG AL...
BC

Dear Dr. Sobel, **APPEARS THIS WAY ON ORIGINAL**

We refer to NDA 20-918 GlucaGen® [glucagon (rDNA)].

We are enclosing in duplicate, the 12 months interim stability report for GlucaGen® (development item #5-1972-05; production no. for US item 5-9400-44) and the supportive 24 month interim stability report. These reports are submitted in support of the expiry dating proposed in the NDA and in response to the CMC Review Comment #16 (March 4, 1998).

APPEARS THIS WAY ON ORIGINAL

Additionally, we are submitting a separate patent information statement indicating no relevant patents. The patent certification in the original NDA indicated the same.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely, **APPEARS THIS WAY ON ORIGINAL**
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph. D.
Vice President, Regulatory Affairs

/mk

Enclosures **APPEARS THIS WAY ON ORIGINAL**

cc: Full copy to Field Office with Field Copy Certification

ORIGINAL

ORIGINAL

NEW CORRESP

(c)

Novo Nordisk



Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

May 5, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857

Re: GlucaGen® [glucagon (rDNA)]
NDA 20-918

APPEARS THIS WAY ON ORIGINAL

Dear Dr. Sobel,

As requested by Ms. Julie Rhee, enclosed are two copies of the fax sent to her on April 29, 1998 regarding the teleconference to discuss the assay validation for Study 101. Also enclosed, are two copies of the list of attendees.

If you have any further questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

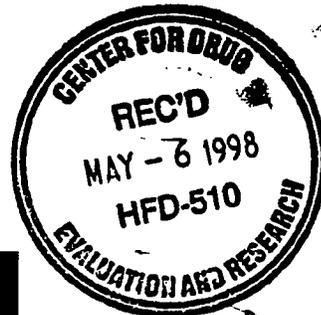
Sincerely,

Mary Ann McElligott

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

Enclosures

*Reviewed
N/A
5/19/98
/sl*



*ASD
5/19/98
/sl*

*10/27/11
/sl*

ORIGINAL

REVIEWS COMPLETED	
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<i>/sl</i>	5-20-98
CSO INITIALS	DATE

NDA ORIG AMENDMENT
ORIGINAL

May 6, 1998

Novo Nordisk

ks/
[Redacted]
6/1/98

Dr. Robert Shore
Food and Drug Administration
CDER/ODEII/DMEDP HFD-510
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



**Novo Nordisk
Pharmaceuticals Inc.**
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: Assay Validation Results for GlucaGen® Study 007
NDA 20-918 GlucaGen® [glucagon (rDNA)]

Dear Dr. Shore,

APPEARS THIS WAY ON ORIGINAL

As discussed last week, we are faxing (hard copy to follow) some initial results from the assay validation for your review. The validation is still ongoing, including inter- and intra-assay validation and storage stability covering the time period of analysis.

We will have those results for you shortly.

Sincerely,

APPEARS THIS WAY ON ORIG

Mary Ann McElligott

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

cc: Julie Rhee

REVIEWS COMPLETED	
CSO ACTION:	
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<input type="checkbox"/> MEMO	5-2-98
CSO INITIALS	DATE

Revised
ks/
[Redacted]
02-30-98

ks/
[Redacted]

APPEARS THIS WAY ON ORIGINAL

ks/
[Redacted]

5/2/98

General Correspondence

NEW CORRESP

April 20, 1998

Dr. William Berlin,
Chemistry Reviewer
CDER/ONDC/DNDCII HFD-520
Parklawn Bldg.
5600 Fishers Lane - Room 14B31
Rockville, MD 20857



Novo Nordisk

Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 20-918
GlucaGen® 1mg [glucagon (rDNA)]

Dear Dr. Berlin,

(b)(4)

This submission should conclude all outstanding issues from the NDA CMC review (fax dated March 4, 1998) and our responses (letter dated March 19, 1998).

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,

APPEARS THIS WAY ON ORIGINAL

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

cc: Julie Rhee

APPEARS THIS WAY ON ORIGINAL

REVIEWS COMPLETED
CSO ACTION:
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<i>m</i> 6-18-98
CSO INITIALS DATE

ORIGINAL

APPEARS THIS WAY ON ORIGINAL

General Correspondence
Information Request

BP

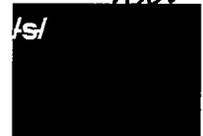
March 17, 1998

Dr. Ron Steigerwalt
Food and Drug Administration
CDER/ODEII/DEMEDP HFD-510
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT
ORIGINAL



Novo Nordisk

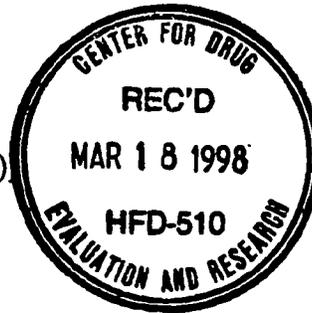


2/24

Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: GlucaGen® [glucagon (rDNA)]
NDA 20-918



Dear Dr. Steigerwalt,

On February 25 we sent you the reports for the Rat and Rabbit Reproduction Studies for GlucaGen® as requested during our telephone conversation of February 23. As discussed today, we are submitting the tabular data listings to supplement those reports.

APPEARS THIS WAY ON ORIGINAL

Please let us know if you need any further information.

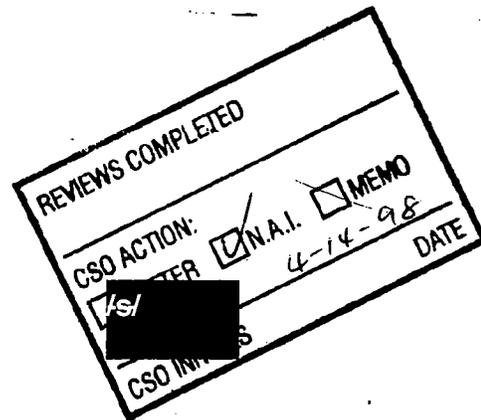
Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

APPEARS THIS WAY ON ORIGINAL

Mary Ann McElligott
Mary Ann McElligott, Ph.D.
Director, Regulatory Affairs

Enclosure

cc: Julie Rhee (w/o enclosure)



F:\.....wpdocs\glucagon\Glucagon - repro studies 3-17-98

APPEARS THIS WAY ON ORIGINAL

NDA ORIG AMENDMENT
ORIGINAL
General Correspondence

Novo Nordisk



Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

March 16, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-918
Glucagen® 1mg [glucagon (rDNA)]

Dear Dr. Sobel,

APPEARS THIS WAY ON ORIGINAL

We refer to NDA 20-918 for Glucagen® 1mg [glucagon (rDNA)]. In response to the biopharm reviewer's request, transmitted by Julie Rhee on February 25, we are submitting additional information for (b)(4)

(b)(4)

This study report was submitted on

March 12, 1998.

(b)(4)

If you have any further questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

APPEARS THIS WAY ON ORIGINAL

Barry Rott, Ph. D.
Vice President, Regulatory Affairs

/mk

Attachment

Handwritten initials and date: 13-111

REVISIONS COMPLETED
CSO ACTION: LETTER N.A.I. MEMO
CSO INITIALS _____ DATE _____

Handwritten initials: MRZ

Handwritten date: 3/24/98

APPEARS THIS WAY ON ORIGINAL

General Correspondence

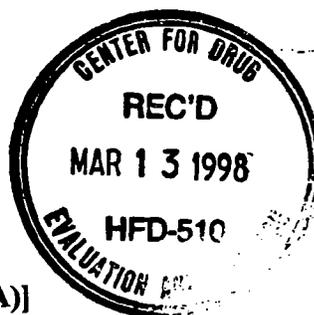
March 12, 1998

NEW CORRESP



Novo Nordisk

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 20-918
GlucaGen® 1mg [glucagon (rDNA)]

Dear Dr. Sobel,

~~APPEARS THIS WAY ON ORIGINAL~~

We refer to NDA 20-918 for GlucaGen® 1mg [glucagon (rDNA)]. In response to the biopharm reviewer's request, transmitted by Julie Rhee on February 25, we are submitting information for Study 101 entitled "A Comparison of the Relative Bioavailability of Glucagon Novo (ge) and Glucagon Novo Given Intramuscularly to Healthy Volunteers". This report was submitted previously in the original IND. We will submit the Assay Validation information for that study on Monday, as discussed.

If you have any further questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

~~APPEARS THIS WAY ON ORIGINAL~~

Barry Reit, Ph. D.
Vice President, Regulatory Affairs

/mk

Enclosure

Notes
1/31

Notes
1/31

3/29/98

~~APPEARS THIS WAY ON ORIGINAL~~

ORIGINAL

ORIGINAL
AMENDMENT

Novo Nordisk



Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082



February 25, 1998

Dr. Ron Steigerwalt
Food and Drug Administration
CDER/ODEII/DMEDP HFD-510
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857

RE: GlucaGen® [glucagon (rDNA)] NDA 20-918
Information on Reproduction Studies

Dear Dr. Steigerwalt,

APPEARS THIS WAY ON ORIGINAL

Enclosed are the reports including tables for the Rat and Rabbit Reproduction Studies for GlucaGen® as requested during our telephone conversation of February 23rd.

Please let us know if you need any further information.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mary Ann McElligott

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
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<i>/sl</i>	3-11-98
CSO INITIALS	DATE

Labeling comments to be faxed as FDA revision #4.

Enclosure

cc: Julie Rhee

Pharm Review on this was completed 3/5/98. There were items to be communicated to the sponsor.

NAT
/sl
3/24/98

General Correspondence

ORIGINAL
BI
AMENDMENT

Novo Nordisk



Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

February 17, 1998

Dr. Brenda Uratani,
Microbiologist
CDER/ONDC/ONDC/HFD-160
Parklawn Bldg., Room 1753
5600 Fishers Lane
Rockville, MD 20857



RE: GlucaGen® 1mg [Glucagon (rDNA)]
NDA 20-918

Dear Dr. Uratani,

APPEARS THIS WAY ON ORIGINAL

As requested in your fax dated February 10, 1998, enclosed is the summary validation data (b)(4) of GlucaGen® 1 mg.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

M.A. McElligott for Barry Reit

Barry Reit, Ph. D.
Vice President, Regulatory Affairs

cc: Julie Rhee

Enclosure
/mk

APPEARS THIS WAY ON ORIGINAL

REVIEWS COMPLETED	
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<i>isl</i>	3-19-98
CSO INITIALS	DATE

NDA under review.

isl
3/19/98

isl
3/19/98

February 13, 1998



Novo Nordisk
ORIGINAL
AMENDMENT

Ms. Julie Rhee,
Consumer Safety Officer
Food and Drug Administration
CDER/ODEII/DMEDP/HFD-510
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: GlucaGen® [glucagon (rDNA)]
NDA 20-918
GlucaGen® Labeling Revision 2

Dear Julie,

APPEARS THIS WAY ON ORIGINAL

We have revised the labeling according to the recommendations of February 6, 1998 made by the Pharmacology Team Leader, Dr. Ronald Steigerwalt. We are attaching the recommendations with identifying numbers and provide a hard copy of the revised Package Insert with the corresponding numbers. We spoke to Dr. Steigerwalt about the fact that reproduction studies were conducted with GlucaGen®. Based on that conversation, the wording is different than originally outlined in the fax.

The electronic version of the insert is enclosed and the file name is as follows:

Novo GlucaGen PI Revision 2

APPEARS THIS WAY ON ORIGINAL

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

M A McElligott

Mary Ann McElligott, Ph.D.
Director, Regulatory Affairs

Enclosure

/mk

REVIEWS COMPLETED
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<i>IS/</i> <i>4-8-98</i>
CSO INITIALS DATE

*Labeling revised
w/IS 2/25/98
w/IS*

IS/

IS/

APPEARS THIS WAY ON ORIGINAL

Handwritten initials and date: 3/11/98

General Correspondence

ORIGINAL

January 29, 1998

Dr. Solomon Sobel
Dir., Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg., Room 14B04
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082



RE: GlucaGen® 1mg [Glucagon (rDNA)]
NDA 20-918

Dear Dr. Sobel,

As requested in your fax dated January 5, 1998, enclosed is the summary data on the validation runs for the sterilization of the following items used in the manufacture of GlucaGen® 1mg:

- Stoppers and utensils
- Preparation tanks
- Equipment (filling equipment, tubing, and manifold which are sterilized by Steam-in-Place, filter and filtration cartridge)
- Lyophilizers
- Vials

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Handwritten signature of Barry Reit

Barry Reit, Ph. D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
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770- 3-19-98
CSO INITIALS DATE

Enclosure
/mk

NDA under review



Novo Nordisk

ORIGINAL
AMENDMENT



Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

January 15, 1998

RE: GlucaGen® NDA 20-918
Electronic copy of Package Insert

Dear Julie,

APPEARS THIS WAY ON ORIGINAL

As requested, enclosed is a disk with the file for the GlucaGen® Draft Package Insert.
The file is a Word file.

APPEARS THIS WAY ON ORIGINAL

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mary Ann McElligott, Ph.D.
Director, Regulatory Affairs

REVIEWS COMPLETED	
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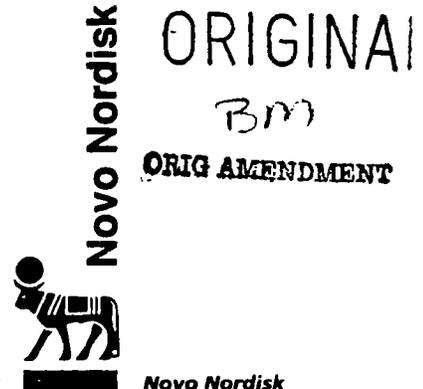
New disk submitted 2-11-98

APPEARS THIS WAY ON ORIGINAL

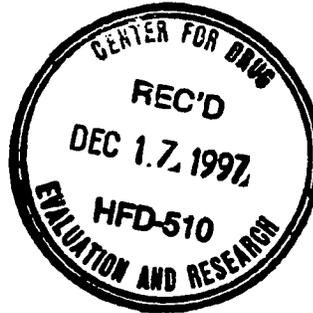
Amendment #1

September 16, 1997

APPEARS THIS WAY ON ORIGINAL



Solomon Sobel
Novo Nordisk, Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Rocklawn Bldg., Room 14B04
100 Fishers Lane
Rockville, MD 20857



Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Reference: NDA 20-918

Dear Dr. Sobel,

The following information is provided in response to Dr. Misbin's query of October 2, 1997 regarding plasma glucagon levels.

If you have any questions, please contact Mary Ann McElligott, Director, Regulatory Affairs at (609) 987-5831.

Sincerely,

M A McElligott for Barry Reit

Barry Reit, Ph. D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
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	12/31/97
CSO I	DATE

Desk copy sent to Dr. Misbin

APPEARS THIS WAY ON ORIGINAL

Noted
ts/
1/97

ORIGINAL

ORIG ALSENDER

Novo Nordisk



Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

November 6, 1997



Dr. Solomon Sobel
Dir., Div. Of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg. Room 14B04
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-918

Dear Dr. Sobel,

We refer to NDA 20-918 for GlucaGen® [glucagon (rDNA)] (b)(4)
(b)(4)

We are submitting responses to the information requests listed in that letter. The enclosed document contains the following:

(b)(4)

If you have any questions, please contact Mary Ann McElligott, Director, Regulatory Affairs at (609) 987-5831.

Sincerely,

Barry Reit, Ph. D.
Vice President, Regulatory Affairs

cc: Dr. Shore

REVIEWS COMPLETED	
CSO ACTION:	
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/s/ [redacted]	11-25-97
CSO INITIALS	DATE

2/s/ [redacted] 17
FAX COPY

APPEARS THIS WAY ON ORIGINAL

20918

ORIGINAL

October 1, 1997

Solomon Sobel, MD
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



**Novo Nordisk
Pharmaceuticals Inc.**
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082



RE: **GlucaGen® (glucagon (rDNA))
505(b)(2) NDA**

APPEARS THIS WAY ON ORIGINAL

Dear Dr. Sobel:

Enclosed is a List of Documents for the GlucaGen® NDA. This list contains all documents, in alphabetical order, that are referred to in the GlucaGen® NDA and gives a cross reference to locations in the NDA. This list may be a useful aid for the reviewer.

If you have any questions or need any further information please contact Dr. Mary Ann McElligott, Director, Regulatory Affairs at (609) 987-5831.

APPEARS THIS WAY ON ORIGINAL

Sincerely,

Mary Ann McElligott

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>m</i> 10-27-97
CSO INITIALS DATE

[Handwritten signature]
/s/ [Redacted]

Enclosure

MAMc/mk

N/A... please...
/s/ [Redacted]

[Handwritten signature]
/s/ [Redacted]
10/1/97

N/R
[Redacted]
10/27/97

September 18, 1997

Solomon Sobel, MD
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

Novo Nordisk
Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: **GlucaGen® (glucagon (rDNA))**
505(b)(2) NDA

Dear Dr. Sobel:

APPEARS THIS WAY ON ORIGINAL

Reference is made to IND 36,913 Glucagon injection (rDNA origin). The GlucaGen® NDA is submitted as a 505(b)(2) application.

The 505 (b)(2) application was discussed with the agency on May 10, 1996 and based on the discussion a clinical summary of Novo Nordisk studies with GlucaGen® was prepared and submitted on November 6, 1996. The clinical summary of Novo Nordisk studies was reviewed by the agency and a bioequivalence study comparing GlucaGen® and the Lilly (b)(4) Glucagon product was requested and conducted. At the time Novo Nordisk conducted the bioequivalence study in the US, it was agreed with Dr. Stephen Moore that the IND would not be updated at that time, but a table outlining the changes, IND to NDA, would be submitted in the NDA (See NDA Section Investigational Product Formulation).

On June 3, 1997 Novo Nordisk met with the agency and discussed a proposal for the format and content of the Glucagon 505(b)(2) NDA.

It was agreed that the 505 (b)(2) NDA would be modified as follows:

- Application Summaries - only summaries pertinent to the submission to be provided: package insert referenced to Novo Nordisk information and literature.

APPEARS THIS WAY ON ORIGINAL

- Clinical Section - composed of the Clinical Summary submitted November 6, 1996 and the Bioequivalence Study Report.

APPEARS THIS WAY ON ORIGINAL

Dr. Solomon Sobel
September 18, 1997
Page 2

It was agreed that the following NDA sections or subsections were not pertinent to the GlucaGen® 1 mg 505 (b)(2) NDA:

Integrated Summary of Safety
Integrated Summary of Efficacy
Benefits and Risk
Non-clinical Pharmacology and Toxicology Technical Section
Human Pharmacokinetics and Bioavailability Technical Section
Statistical Technical Section
Case Record Forms and Tabulations

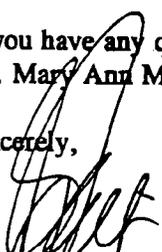
We intend to market this product under the trade name of GlucaGen® (glucagon (rDNA)).

APPEARS THIS WAY ON ORIGINAL

This original application is being submitted in triplicate (archive copy, review copy, and field copy).

If you have any questions regarding the contents of this submission, please contact Dr. Mary Ann McElligott, Director, Regulatory Affairs.

Sincerely,


Barry Reit, Ph.D.
Vice President, Regulatory Affairs

BR/pk
f:\.....\glucagon\nda

APPEARS THIS WAY ON ORIGINAL