

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020918

PHARMACOLOGY REVIEW(S)

Labeling comments
based as FDA revision #4

RNEE

MAR -9 1998

NDA 20-918

Review Completed: March 9, 1998

Sponsor: Novo Nordisk Pharmaceuticals, Inc.; Princeton, NJ 08540

Date Submitted: February 25, 1998

Date Received: February 26, 1998

DRUG: GlucaGen® [glucagon (rDNA)]

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Isl

Ronald W. Steigerwalt, Ph.D.

3/9/98

cc: IND Arch
HFD510
HFD510/Steigerwalt/J.Rhee/H.Rhee

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NDA 20-918

Review Completed: March 9, 1998

Sponsor: Novo Nordisk Pharmaceuticals, Inc.; Princeton, NJ 08540

Date Submitted: February 25, 1998

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**PHARMACOLOGY REVIEW OF NDA SUBMISSION
NDA 20-918 (February 26, 1998)**

DRUG: GlucaGen® [glucagon (rDNA)]

STRUCTURAL FORMULA: 29 amino acid rDNA identical to naturally occurring human glucagon and to glucagon extracted from beef and pork pancreas. MW 3483

INDICATION: To treat severe hypoglycemic reactions and as a diagnostic to inhibit g.i. movement.

MEMOS: Sponsor had originally provided only summaries of DART studies. In order to include the findings in the label, I requested that the sponsor provide translations of the studies and tabular listings. These are the subject of this review.

REVIEW OF STUDY 9K109:
A STUDY ON INTRAVENOUS ADMINISTRATION OF GLUCAGON (GE) TO RABBITS
DURING THE PERIOD OF FETAL ORGANOGENESIS

NOTE: This is an unaudited draft report from (b)(4)

(b)(4)

Lot # G4491813, purity over 98%.

1.1 IU/mg.

PURPOSE: To study the teratogenic effects and effects on does due to IV administration of glucagon to rabbits during the period of fetal organogenesis. Studies performed April 1989-August 1989.

EXPERIMENTAL DESIGN: 0, 0.4, 2.0 and 10 mg/kg/day was administered to female Japanese albino stock rabbits (SPF) (16/group) from day 6-day 18 of pregnancy by continuous IV drip. Males used in breeding were 6 months old. Females were 5 months old (b)(4) Food was available *ad lib*. All animals were necropsied on day 29 of pregnancy. Non-pregnant animals were not considered in data analysis.

DOSE SELECTION JUSTIFICATION: Preliminary study of doses of 2.5, 5 and 10 mg/kg in pregnant rabbits indicated significant difference in embryo mortality after implantation in the 10 mg/kg group. Since implantation in rabbits coincided with initiation of dosing, 10 mg was considered to affect the maintenance of pregnancy following implantation.

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RESULTS

MATERNAL OBSERVATIONS

CLINICAL SIGNS: Loose feces noted without dose relationship. Decrease in spontaneous movement and tachypnea was observed in 1 high dose animal on day 8. Repeated symptoms of decreased spontaneous movement and tachypnea were observed in 9 cases from day 13-18 of pregnancy. These generally recovered quickly after dosing. However, in three cases (one animal not pregnant) these did not recover from these symptoms and progressed to death.

MORTALITY: 2 HD animals (1 not pregnant) died after decreased movement and tachypnea was observed on day 16. A third doe died on day 17 of pregnancy.

BODY WEIGHT/FOOD INTAKE: Body weight decreased in 1-2 animals of each group after day 6 or 12 of pregnancy. MD and HD animals did not recover weight by time of necropsy. No significant change in food intake was observed between groups. Individual observations revealed that one high dose animal did not eat after day 12 of pregnancy.

FINDINGS AT NECROPSY: No treatment-related effects were observed. Non-pregnant animals were found in control (3), LD(2), MD (4), and HD (1 animal that died on test). No treatment related findings were observed in number of corpora lutea, implantations, number of deaths after implantation (early or late deaths), number of living fetuses, sex ratio, fetal body weights or death rates of embryos.

FETAL OBSERVATIONS

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EXTERNAL OBSERVATIONS: Findings of malformations were limited to two litters in the high dose groups. The does with these litters exhibited decreased activity and tachypnea in response to the treatment. One had not eaten after day 12. These fetal findings may be attributable to maternal toxicity.

APPEARS THIS WAY ON ORIGINAL

TABLE 1: EXTERNAL OBSERVATIONS:

DOSE (mg/kg) - OBSERVATION ↓	CONTROL	0.4	2.0	10.0
Number of does	13	14	12	13
Number of fetuses	101	100	86	80
Abnormal fetuses	2.6 ² (1/1) ³	- ⁴	-	12.5 (12/2)
Ecaudate fetus	2.6 (1/1)	-	-	-
Cleft palate	-	-	-	3.2(3/2)
Malformation of fingers	-	-	-	3.3 (3/1)
Crooked tail	-	-	-	3.3 (3/2)
Manus vara	-	-	-	4.4 (4/1)
Cleavage of palpebra	-	-	-	9.3 (9/2)
Clubfoot (separation of tibia and fibula)	-	-	-	7.7 (7/1)

1. fetuses with malformations or teratologies
2. mean incidence (%)
3. Number of abnormal fetuses/number of does with abnormal fetuses
4. No incidence of abnormalities

APPEARS THIS WAY ON ORIGINAL

INTERNAL ORGAN EXAMINATION: Only high dose group and controls were listed in table.

TABLE 2: INTERNAL ORGAN OBSERVATIONS

DOSE (mg/kg) → OBSERVATION ↓	CONTROL	10.0
Number of does	12	10
Number of fetuses	43	35
Abnormal fetuses ¹	11:7 ² (6/3) ³	7.5 (3/3)
[Malformation]		
Cervical residue of thymus	2.1 (1/1)	- ⁴
Accessory coronary artery ostium	7.9 (4/3)	5.0 (2/2)
[Teratology]		
Ventricular septal defect	1.7 (1/1) ⁵	-
Truncal stenosis	1.7 (1/1) ⁵	-
Accessory renal artery	-	2.5 (1/1)

APPEARS THIS WAY ON ORIGINAL

1. fetuses with malformations or teratologies
2. mean incidence (%)
3. Number of abnormal fetuses/number of does with abnormal fetuses
4. No incidence of abnormalities
5. Simultaneous development in same fetus

SKELETAL EXAMINATION: No treatment-related findings were detected between controls and high dose. LD and MD groups were not examined.

MALFORMATIONS AND TERATOLOGIES OF SKELETON: Control and HD examined. No treatment-related differences were observed. LD and MD were not examined.

TABLE 3: SKELETAL MALFORMATIONS AND TERATOLOGIES

DOSE (mg/kg) → OBSERVATION ↓	CONTROL	10.0
Number of does	13	11
Number of fetuses	58	45
Number of abnormal fetuses ¹	32.2 ² (18/10) ³	41.4 (18/7)
[Malformation]		
13 th rib	25.9 (14/8)	26.2 (12/5)
Nonsymmetrical sternebra	3.8 (2/2)	5.3 (2/2)
Bilateral division of sternebra	4.7 (3/3)	10.2 (4/3)
Excess sternebra	1.5 (1/1)	3.0 (1/1)
Aplasia of parietal bone	- ⁴	12.9 (5/2)
Aplasia of interparietal bone	-	1.5 (1/1)
Cleavage between cervical vertebral arches	-	3.0 (1/1)
[Teratology]		
Fusion of sternebra	-	3.0 (1/1)
Missing caudal vertebra	3.8 (1/1)	-
Separation of tibia and fibula	-	9.1 (3/1)

APPEARS THIS WAY ON ORIGINAL

1. fetuses with malformations or teratologies
2. mean incidence (%)
3. Number of abnormal fetuses/number of does with abnormal fetuses
4. No incidence of abnormalities

APPEARS THIS WAY ON ORIGINAL

EVALUATION

Condition of does: Treatment-related clinical signs consisted of decrease in spontaneous movement and tachypnea in the high dose group during or immediately after drug administration. In most cases, recovery was rapid. In three cases out of nine, animals did not recover and eventually died. These symptoms were confirmed in a separate study in non-pregnant animals at 2 times the HD in the present study. At 15 mg/kg, animals presented with procumbent position, dyspnea and soon progressed to death. Therefore, the high dose chosen for the reproduction studies is adequate and in some cases caused excessive toxicity to the does. The sponsor hypothesized that the death was due to a decrease in arterial blood pressure and increase in heart rate related to the pharmacological effects of the drug, but could not establish a clear relationship. There were no clear treatment-related histopathological findings.

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Fetal Abnormalities are listed in Table 1. The listed abnormalities were not observed during a preliminary dose selection study. The malformations and teratologies were found only in the high dose group. Skeletal abnormalities occurred primarily in fetuses that also exhibited external abnormalities. The abnormal fetuses in this rabbit study were concentrated in the 2/13 does which exhibited sensitivity to the treatment as described in the clinical signs section.

Published studies in rats indicated findings of cataracts, microphthalmia, glaucoma-type eye malformation, or abnormalities of the tail or skeletal structure (torsion of the central skeletal structure) (S. Scaglioni Folia. Hered. Pathol. 9: 143, 1960 and Tuchmann-Duplessis and Mercier-Parot C.R. Acad. Sci. (Paris) 254: 2655, 1962). These findings were not observed in this rabbit study.

APPEARS THIS WAY ON ORIGINAL

Under the conditions of this study (IV drip administration from days 6-18 of pregnancy), 10.0 mg/kg administered to rabbits during the period of fetal organogenesis caused maternal toxicity in some animals. Most malformations and teratologies were detected in does exhibiting toxicity. There was no apparent relationship of treatment and fetal effects in does without maternal toxic observations.

APPEARS THIS WAY ON ORIGINAL

**REVIEW OF STUDY 9K108:
A STUDY ON INTRAVENOUS ADMINISTRATION OF GLUCAGON (GE) TO RATS DURING
THE PERIOD OF FETAL ORGANOGENESIS**

NOTE: This is an unaudited draft report from (b)(4)

(b)(4)

Lot # G4491813, purity over 98%.

1.1 IU/mg.

PURPOSE: To study the teratogenic effects and effects on dams due to IV administration of glucagon to rats during the period of fetal organogenesis. Additionally, effects on fetal behavioral function and reproductive function were assessed. Studies performed April 1989-October 1989.

EXPERIMENTAL DESIGN: 0, 0.4, 2.0 and 10 mg/kg/day was administered to female SD (Crj:CD)(SPF) rats (24/group for Cesarean and 10/group for natural birth) from day 7-day 17 of pregnancy by to the caudal vein between 9:00-12:00h. (In the summary, it is described as IV drip 4 ml/min). Food was available *ad lib*. Cesarean animals were necropsied on day 29 of pregnancy. Non-pregnant animals were not considered in data analysis. Natural birth dams were allowed to nurse pups until day 21 post partum. Non-delivering dams were necropsied on day 25 post partum. ~~APPEARS THIS WAY ON ORIGINAL~~

DOSE SELECTION JUSTIFICATION: Preliminary study of doses of 2.5, 5 and 10 mg/kg in pregnant rats (6/group). There was a slight inhibition of weight gain in the high dose group. Thus, 10 mg/kg was chosen as the high dose group for the definitive study. Lower doses were chosen as the "common ratios" that is generally standard procedure in Japan. Thus, doses for the definitive study were defined as 0, 0.4, 2.0 and 10 mg/kg/day.

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RESULTS

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MATERNAL OBSERVATIONS

CLINICAL SIGNS: 1 HD dam had "discoloration of the eyes" which was not specifically described after day 16 of pregnancy. This animal also exhibited transient tachypnea after dose administration on day 16 and 17 (animal #D28). Another HD dam had subcutaneous nodules in the lower abdomen after day 13 of pregnancy. There were no specific abnormalities of the fetuses from this dam.

MORTALITY: There were no unscheduled mortalities.

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BODY WEIGHT/FOOD INTAKE: Inhibition of weight gain after the middle term of pregnancy was observed in the HD group. This was statistically significant on day 17 and 20 of pregnancy. There was no decrease in body weight at parturition or during nursing. Animal number D28 (see above) presented with markedly small weight gain and food intake. Excluding this single animal, there was not significant change in body weights or food intake..

FINDINGS AT NECROPSY: Animal D28 (see above) exhibited severe atrophy of the thymus, slight swelling of the accessory lymph nodes, congestion as well as atelectasis and gray lesions in the lungs. Arterial thrombosis-suspected due to metastasis of a yolk sac tumor to the lungs

and acute thymus atrophy were observed. Animal D23 presented with subcutaneous nodules diagnosed as mastadenoma. There were no other effects observed at Cesarean or weaning. At Cesarean section, one animal each in the control group, LD and 2 in the MD group did not have confirmed implantations. Data from these animals was excluded from the study.

FETAL OBSERVATIONS: CESAREAN DELIVERY

TABLE 1: CESAREAN OBSERVATIONS:

APPEARS THIS WAY ON ORIGIN

DOSE (mg/kg) → OBSERVATION ↓	CONTROL	0.4	2.0	10.0
# Dams Examined	22	22	21	23
# Corpora Lutea	17.9	17.3	17.2	17.1
# Implantations	16.2	15.8	15.1	15.2
#Deaths After Implantation (Early Deaths; Note: There Were No Late Deaths In Any Group)	0.9	0.8	0.7	1.0
# Surviving Fetuses	15.3	15.0	14.4	14.3
Gender Ratio (M/F)	0.95	0.88	1.10	1.16
Fetal Body Weight (Male)	3.23	3.29	3.23	3.13
Fetal Body Weight (Female)	3.06	3.08	3.08	2.93
Death Rate Prior To Implantation	8.0	8.1	11.2	10.7
Death Rate After Implantation	5.6	5.1	5.3	6.2
Total Death Rate	13.1	12.8	15.6	16.1

EXTERNAL OBSERVATIONS: One HD fetus had systemic edema; no other abnormalities were observed in other fetuses.

TABLE 2: INTERNAL ORGAN EXAMINATION: Only high dose group and controls were listed

DOSE (mg/kg) → OBSERVATION ↓	CONTROL	10.0
Number of dams	22	23
Number of fetuses	161	160
Abnormal fetuses ¹	20.0 ² (31/13 ³)	21.6 (35/17)
[Malformation]		
Cervical residue of thymus	6.7 (16/6)	9.5 (15/8)
Left umbilical artery	2.4 (4/4)	1.1 (2/2)
Pyelectasis	9.5 (15/9)	7.1 (12/8)
[Teratology]		
Atrial septal defect	2.1 (3/3)	1.2 (2/2)
Ventricular septal defect	0.8 (1/1)	1.2 (2/2)
Cardiac deformity	0.8 (1/1)	2.1 (3/2)
Dextroposition of heart	1.1 (2/1)	2.3 (3/3) ⁵
Partial visceral inversion	- ⁴	0.6 (1/1) ⁵
Fusion of pulmonary fissure	-	0.6 (1/1) ⁵
Patent common atrioventricular canal	-	0.6 (1/1) ⁵
Abnormality of lobulation of liver	-	0.6 (1/1) ⁵
Total visceral inversion	-	0.6 (1/1) ⁵

APPEARS THIS WAY ON ORIGIN

1. fetuses with malformations or teratologies
2. mean incidence (%)
3. Number of abnormal fetuses/number of dams with abnormal fetuses
4. No incidence of abnormalities
5. Simultaneous development in same fetus

Special note: Published studies indicated a finding of glaucoma-like findings in a rat teratology study with pancreatic glucagon. There were no such findings in the present study.

SKELETAL EXAMINATION: Significant decrease in sternum number in the HD group. Markedly slow bone formation was observed only in the fetuses of the mother for which the yolk sac tumor was suspected. Progress was clearly slower compared to other fetuses. This was attributed to maternal condition. When this fetus was removed from data analysis, mean progress of bone formation number of the sternum in the HD group was 5.43 and a significant difference between the control group was not observed. MD and LD groups were also examined and no significant difference was determined from controls.

MALFORMATIONS AND TERATOLOGIES OF SKELETON:

APPEARS THIS WAY ON ORIGINAL

TABLE 3: SKELETAL MALFORMATIONS AND TERATOLOGIES

DOSE (mg/kg) → OBSERVATION ↓	CONTROL	10.0
Number of dams	22	23
Number of fetuses	175	168
Number of abnormal fetuses ¹	27.5 ² (46/17) ³	25.0 (43/21)
[Malformation]		
Sacralization of lumbar vertebra	0.6 (1/1)	- ⁴
Nonsymmetrical sternal nucleus	-	0.5 (1/1)
Separation of ossification nucleus of 13 th rib	-	0.5 (1/1)
14 th rib	1.8 (3/3)	1.1 (2/2)
Shortening of 13 th rib	1.0 (2/2)	1.1 (2/2)
Bilateral division of ossification nucleus of the vertebral body	0.8 (2/2)	1.2 (2/2)
Closure of foramen of the transverse process of the cervical vertebral arch	22.3 (37/15)	18.8 (32/17)
Presacral 25 th vertebra	0.5 (1/1)	-
Cervical rib	-	1.1 (2/1)
Excess hypoglossal foramen	1.1 (2/1)	0.5 (1/1)
[Teratology]		
Fusion of sternbra	-	-
Missing caudal vertebra	-	-
Separation of tibia and fibula	-	-

1. fetuses with malformations or teratologies
2. mean incidence (%)
3. Number of abnormal fetuses/number of dams with abnormal fetuses
4. No incidence of abnormalities

APPEARS THIS WAY ON ORIGINAL

FETAL OBSERVATIONS: NATURAL DELIVERY

PARTURITION FINDINGS: No treatment-related abnormalities were noted in the following: Parturition rate, Delivery rate (survival after implantation), Parturition, Suckling, Nest-making, Nursing.

APPEARS THIS WAY ON ORIGINAL

IMPLANTATION RATE: Number of implantations was significantly low in MD and HD groups, but was considered not likely due to drug administration since treatment did not commence until after implantation.

APPEARS THIS WAY ON ORIGINAL

MORTALITY: One HD female drown in water trough on day 2 of pregnancy. This animal was excluded from analysis. 1 LD female did not deliver (examination on day 25 post coitus indicated that implantation had not occurred). Data from this animal was also excluded from analysis.

APPEARS THIS WAY ON ORIGINAL

GENERAL CONDITION OF FETUSES: No treatment-related abnormalities.

SURVIVAL RATE: Significant decrease in number of live births in the HD as well as in the number of surviving fetuses prior to adjustment 4 days after birth. However, the number of dead pups was small and there was not a significant difference in survival rate. No changes in gender ratio or weaning rate was noted.

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FETAL BODY WEIGHT: No treatment-related effects.

MORPHOLOGICAL DIFFERENTIATION: Significant delay in opening of the external acoustic meatus in LD males and in MD males and females. Cleavage of palpebra were significantly early among males in the HD group. These findings were not considered treatment-related.

REFLEX RESPONSES: No clear treatment-related findings. Control group responses were low, dose dependency could not be established.

BEHAVIORAL EXAMINATION: No treatment related findings in motor coordination or learning ability.

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POSTMORTEM OF F1 PUPS: No treatment-related findings in organ weights or gross pathology. There was an increase in thyroid weights in LD males and in heart weight of HD males, but this was not evident when comparing organ weights relative to body weights.

REPRODUCTIVE PERFORMANCE OF F1 PUPS: No treatment-related effects were evident. HD female F1 group had significantly decreased body weight during day 7-20 of pregnancy. Specific data were not provided.

CESAREAN EXAMINATION OF F1 DAMS: No treatment-related effects on # corpus lutea, # implantations, # dead embryos, # surviving fetuses, sexual ratio, body weight of surviving fetuses, death rate of embryos. 1 HD F2 fetus had external cephalus, bilateral open palpebra and vestigial tail. This was not clearly treatment-related.

EVALUATION

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CLINICAL SIGNS: Treatment-related maternal toxicity was relatively mild. One HD female exhibited transient tachypnea consistent with findings in rabbits sensitive to the effects of glucagon. This animal also had a markedly small weight gain and food intake and was also determined to have a yolk sac tumor. When removed from analysis, there was no significant change induced by treatment. This did not lead to death. No treatment-related clinical signs were evident in F1 or F2 pups.

APPEARS THIS WAY ON ORIGINAL

FETAL OBSERVATIONS: There was a significant increase in death rate prior to implantation in F1 fetuses. Since treatment began after implantation, this was determined not to be a treatment-related effect. There was a slight decrease in fetal body weights. However, this was

primarily due to findings in the fetuses from the dam that was determined to have the yolk sac tumor and thus are likely due to poor maternal condition. When eliminated from the analysis, there was no treatment-related effect on F1 fetal body weights noted. There were no treatment-related findings in the internal organ examination of F1 fetuses. There were no treatment-related effects on morphological differentiation, reflex responses, behavioral examinations or reproductive performance of F1 pups.

APPEARS THIS WAY ON ORIGINAL

Under the conditions of this study (IV administration from days 7-17 of pregnancy), 10.0 mg/kg administered to rats during the period of fetal organogenesis caused slight maternal toxicity in some animals. There were no treatment-related malformations or teratologies detected. There was no apparent relationship of treatment and fetal effects.

There is a report (Holloway and Stevenson, Can. J. Physiol. Pharmacol. 43: 473, 1965) of decreased fetal weight and an increase in absorbed fetuses in a study where dams were administered 1 mg/kg glucagon b.i.d. during day 7-13 of pregnancy. The decreased fetal weights were not observed in this study except for fetuses from one dam that had a yolk sac tumor and exhibited poor condition. The decreased in number of pups in this study reflected the decreased implantations that occurred prior to the initiation of dosing rather than a treatment-related effect.

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OVERALL EVALUATION OF DART STUDIES

Since implantation in rabbits coincided with initiation of dosing, 10 mg was considered to affect the maintenance of pregnancy following implantation in rabbits.

Published studies in rats indicated findings of cataracts, microphthalmia, glaucoma-type eye malformation, or abnormalities of the tail or skeletal structure (torsion of the central skeletal structure) (S. Scaglione Folia. Hered. Pathol. 9: 143, 1960 and Tuchmann-Duplessis and Mercier-Parot C.R. Acad. Sci. (Paris) 254: 2655, 1962). These findings were not observed in these studies. Another study in rats (Holloway and Stevenson, Can. J. Physiol. Pharmacol. 43: 473, 1965) reported decreased fetal weight and an increase in absorbed fetuses in a study where dams were administered 1 mg/kg glucagon b.i.d. during day 7-13 of pregnancy. The decreased fetal weights were not observed in this study and the decreased in number of pups in this study reflected the decreased implantations that occurred prior to the initiation of dosing rather than a treatment-related effect. It is possible that these differences result either from strain differences or differences in treatment (slow IV infusions vs SC dosing).

Under the conditions of the rabbit study (IV drip administration from days 6-18 of pregnancy), 10.0 mg/kg administered to rabbits during the period of fetal organogenesis caused maternal toxicity in some animals. Most malformations and teratologies were detected in does exhibiting toxicity. There was no apparent relationship of treatment and fetal effects in does without maternal toxic observations.

APPEARS THIS WAY ON ORIGINAL

Under the conditions of the rat study (IV drip administration from days 7-17 of pregnancy), 10.0 mg/kg administered to rats during the period of fetal organogenesis caused mild maternal toxicity in some animals. Decreased fetal weights were detected in a single dam exhibiting poor maternal condition (yolk sac tumor). There was no apparent relationship of treatment and fetal effects in dams without maternal toxic observations.

TO BE COMMUNICATED TO SPONSOR

The following label changes should be incorporated into the label: (additions are bolded, deletions are strikeout.)

Pregnancy-Pregnancy Category B- Reproduction studies were **(b)(4)** performed in rats and rabbits at **(b)(4)** GlucaGen® doses of **0.4, 2.0 and 10 mg/kg**. These doses represent exposures of up to 100 and 200 times the human dose based on mg/m² for rats and rabbits, respectively, and **(b)(4)** revealed no evidence of **(b)(4)** or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **(b)(4)**

(b)(4)

(b)(4)

Ronald W. Steigerwalt, Ph.D.

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NDA20-918

Feb. 5, 1998

Novo Nordisk Pharmaceutical, Inc.
Princeton, New Jersey 08540
609-987-5800

Submission: 9/18/1997

Received : 1/5/1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Drug: GlucaGen(rDNA Glucagon)

Related: (b)(4)

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RECOMMENDATION: Pharmacology recommends approval of GlucaGen for the proposed indication with labeling revision.

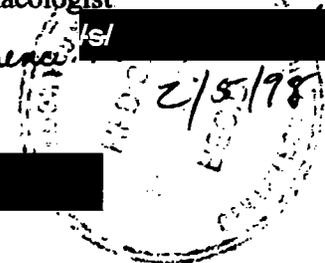
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isl

Herman M. Rhee, Ph.D.
Pharmacologist

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

Concurrence: isl



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NDA20-918

Feb. 5, 1998

Novo Nordisk Pharmaceutical, Inc.
Princeton, New Jersey 08540
609-987-5800

Submission: 9/18/1997

Received : 1/5/1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Drug: GlucaGen(rDNA Glucagon)

Related: (b)(4)

Pharmacological Class: Hypoglycemic and diagnostic test

1. Background to the NDA :

The sponsor discussed with this Division on May 10, 1996 as to 505(b)(2) application. Based on the agreement the sponsor eliminated Non-clinical Pharmacology and Toxicology Technical Section in the present NDA. The preclinical toxicology of the drug has been reviewed during IND phase (b)(4). In addition to the pre-clinical pharmacological studies that were performed by the sponsor, this division requested a dog study at 25 times the human dose to exclude acute cardiac effects on June 30, 1993 and on March 7, 1996 since glucagon is known to produce tachycardia with positive inotropism.

II. Pharmacology:

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1. A Single Dose Toxicity Study: Five Wistar rats/sex/group received glucagon USP or Novo glucagon intravenously at doses of 0, 11, 33, and 100 mg/kg. There was no remarkable difference between the two glucagon preparations.
2. Acute Toxicity Study in Mice: Five NMRI mice/sex/group were administered glucagon USP or Novo glucagon intravenously at doses of 0, 12.5, 50, and 200 mg/kg/day. One female in mid-dose group died.

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3. Effects of GlucaGen on Cardiovascular and Respiratory Function in Conscious Dogs

- a. Test Substance: Lot was not specified. One mg/ml glucaGen solution containing lactose(107 mg/ml) was solubilized in de-ionized water(pH 2.7).
- b. Methods: Three beagle dogs /sex/group were administered GlucaGen or conventional glucagon intravenously at doses of 0(Control), 1 and 5 mg /kg over 15 min period as shown below for 4 weeks. The dose is approximately 250 times of clinical dose (1 mg for 50 kg man, 0.02 mg/kg). Heart rate, electrocardiogram and blood pressure were measured .

Group	Treatment	Dose	# of Male	# of Female
1	Control	0	3	3
2	rGlucaGen	5	3	3
3	Glucagon	1	3	3
4	Glucagon	5	3	3

- c. Results: There was no mortality during the study. There were no treatment-related differences in body weight gain and in food consumption, although there was a higher incidence of soft and loose stool. No treatment-related ocular changes were noted and there were no differences in the hematological parameters between the treated and control groups.
- d. Plasma glucose levels of all treated animals were markedly raised five minutes after dose administration but had fallen back to the normal range within 2 hours.
- e. There was a significant increase in heart rate in the group 2 and 4 animals shortly after dose administration weeks 1 and 4(Please see table 5). There was an increase in blood pressure in treated-animals. But the changes in heart rate and blood pressure between the two groups of animals were not significant. _
- f. The mean, absolute, and relative liver and kidney weights of all the treated groups were higher than those of the controls. There was no gross or histopathological evidence of toxicity of any of the organs and tissues examined.

III. Labeling: Glucagon should be used cautiously to patients with a history of suggestive insulinoma, pheochromocytoma, or both. Pregnancy category B- Reproduction studies have been performed in rats and rabbits at doses up to 700 times the human dose without clear adverse effects. No carcinogenesis studies were performed because glucagon is usually administered in a single dose and have a very short half-life. But, mouse micronucleus test indicated that glucagon did not increase the number of micronuclei in females. Local irritation toxicity was studied in rabbit at doses up to 1 mg glucagon administered and have revealed no evidence of local irritation. For more relevant issues on labeling, please see "Recommend Section" below.

IV. Summary:

The physiology and pharmacology of glucagon has been extensively documented, of which primary effect is elevation of blood glucose through stimulation of glycogenolysis and gluconeogenesis. Glucagon also has catabolic effects on triglycerides and protein metabolism, increased heart rate, positive inotropism, diuresis, anti-inflammatory effects and inhibition of gastrointestinal spasm. The toxicology and pharmacodynamics of GlucaGen following daily intravenous administration were monitored in 4-week CD rat and beagle dog studies. In both species, there were no treatment-related toxicities at doses up to 5.0 mg/kg/day.

~~APPEARS THIS WAY ON ORIGINAL~~

The safety of GlucaGen was profiled in acute studies in rats, in 2-week subchronic toxicology studies in rats and dogs, in a cardiovascular study in dogs, and in the mouse micronucleus assay. Acute toxicity was studied in wistar rats. Five rats/sex were administered a single intravenous or subcutaneous 200 mg/kg of GlucaGen or glucagon USP. No deaths were observed and there was no difference of toxicological potency between GlucaGen and glucagon USP.

~~APPEARS THIS WAY ON ORIGINAL~~

In dogs, increased heart rate was observed following intravenous administration of 5 mg/kg/day. There were no treatment-related differences in body weight gain and in food consumption. No treatment-related ocular and hematological changes were noted. The mean, absolute, and relative liver and kidney weights of all the treated groups were higher than those of the controls. There was no gross or histopathological evidence of toxicity of any of the organs and tissues examined.

~~APPEARS THIS WAY ON ORIGINAL~~

The mutagenic potential tested in the Ames and human lymphocyte assays, was borderline positive. In vivo, high dose (100 and 200 mg/kg) gave a higher incidence of micronucleus formation in male mice. But the weight of evidence indicates that GlucaGen is not different from glucagon pancreatic origin.

V. Recommendation: Letter to the sponsor

~~APPEARS THIS WAY ON ORIGINAL~~

- a. Drug exposure comparisons between preclinical and clinical doses should be based on plasma concentration, AUC or mg/m^2 , rather than on mg/kg . References to comparative exposures in the carcinogenesis and pregnancy categories should be revised to reflect this. For example: "Reproduction studies have been performed in rats and rabbits with glucagon at doses up to xxx times the human dose (based on mg/m^2)...."

~~APPEARS THIS WAY ON ORIGINAL~~

VI. Attachment:

1. Original IND review dated 6/4/1991
2. Review of Amendment (Serial#011) dated 3/7/1996
3. Divisional communication dated 6/30/1993
4. Tables 5 and 6.

APPEARS THIS WAY ON ORIGINAL

RECOMMENDATION: Pharmacology recommends approval of GlucaGen for the proposed indication with labeling revision.

APPEARS THIS WAY ON ORIGINAL

/s/

Herman M. Rhee, Ph.D
Pharmacologist

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

APPEARS THIS WAY ON ORIGINAL