# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

# 20-918/S-003

***Trade Name:*** GlucaGen

***Generic Name:*** (glucagon [rDNA origin] for injection)

***Sponsor:*** Novo Nordisk Pharmaceuticals, Inc.

***Approval Date:*** July 11, 2002

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

## 20-918/S-003

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-918/S-003**

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-918/S-003

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

Please refer to your supplemental new drug application dated July 19, 2001, received July 20, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GlucaGen (glucagon [rDNA origin] for injection).

We acknowledge receipt of your submissions dated July 26 and August 20, 2001, and June 6, 2002.

This "Changes Being Effected" supplemental new drug application proposes to add a statement in the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the package insert that a patient should be given oral carbohydrates as soon as the diagnostic procedure is completed to prevent occurrence of secondary hypoglycemia.

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

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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David Orloff
7/11/02 06:48:59 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-918/S-003**

# LABELING

# GlucaGen®

[glucagon (rDNA origin) for injection]

**Rx ONLY**

## DESCRIPTION

GlucaGen® [glucagon (rDNA origin) for injection] manufactured by Novo Nordisk A/S is produced by expression of recombinant DNA in a *Saccharomyces cerevisiae* vector with subsequent purification.
The chemical structure of the glucagon in GlucaGen® is identical to naturally occurring human glucagon and to glucagon extracted from beef and pork pancreas. Glucagon with the empirical formula of $C_{153}H_{225}N_{43}O_{49}S$, and a molecular weight of 3483, is a single-chain polypeptide containing 29 amino acid residues. The structure of glucagon is:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-
1 2 3 4 5 6 7 8 9 10 11

Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
12 13 14 15 16 17 18 19 20 21 22

Val-Gln-Trp-Leu-Met-Asn-Thr
23 24 25 26 27 28 29

GlucaGen® 1 mg (1 IU) is supplied as a sterile, lyophilized white powder in a 2 ml vial, alone, or accompanied by Sterile Water for Reconstitution (1 ml) also in a 2 ml vial. Glucagon, as supplied at pH 2.5-3.5, is soluble in water.

**Active Ingredient in each vial**
Glucagon as hydrochloride 1 mg (corresponding to 1 IU).

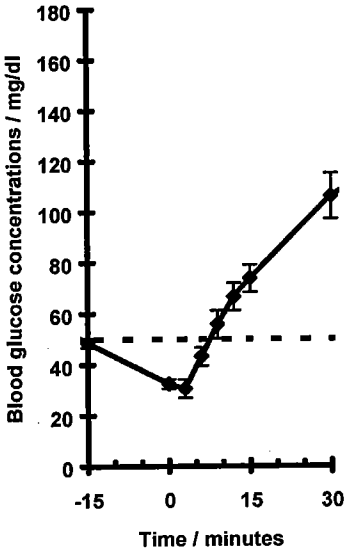
**Other Ingredients**
Lactose monohydrate (107 mg)

When the glucagon powder is reconstituted with Sterile Water for Reconstitution (if supplied) or with Sterile Water for Injection, USP, it forms a solution of 1 mg (1 IU)/ml glucagon for subcutaneous (sc), intramuscular (im), or intravenous (iv) injection.
GlucaGen® is an antihypoglycemic agent, and a gastrointestinal motility inhibitor.

## CLINICAL PHARMACOLOGY

Intramuscular (IM) injection of GlucaGen® resulted in a mean $C_{max}$ (CV%) of 1686 pg/ml (43%) and median $T_{max}$ of 12.5 minutes. The mean apparent half-life of 45 minutes after IM injection probably reflects prolonged absorption from the injection site. Glucagon is degraded in the liver, kidney, and plasma.[1]
*Antihypoglycemic Action:* Glucagon induces liver glycogen breakdown, releasing glucose from the liver. Blood glucose concentration rises within 10 minutes of injection and maximal concentrations are attained at approximately a half hour after injection (see Figure). Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect.

**Recovery from insulin induced hypoglycemia (mean blood glucose) after i.m. injection of 1 mg GlucaGen® in Type I diabetic men**




**Gastrointestinal Motility Inhibition:** Extra hepatic effects of glucagon include relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon.

## INDICATIONS AND USAGE

*For the treatment of hypoglycemia:* GlucaGen® is used to treat severe hypoglycemic (low blood sugar) reactions which may occur in patients with diabetes treated with insulin.
Because GlucaGen® depletes glycogen stores, the patient should be given supplemental carbohydrates as soon as he/she awakens and is able to swallow, especially children or adolescents.
Medical evaluation is recommended for all patients who experience severe hypoglycemia.
*For use as a diagnostic aid:* GlucaGen® is indicated for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract. Glucagon is as effective for this examination as are the anticholinergic drugs. However, the addition of the anticholinergic agent may result in increased side effects. Because GlucaGen® depletes glycogen stores, the patient should be given oral carbohydrates as soon as the procedure is completed.

## CONTRAINDICATIONS

Glucagon is contraindicated in patients with known hypersensitivity to glucagon or any constituent in GlucaGen® and in patients with pheochromocytoma or with insulinoma.

## WARNINGS

GlucaGen® should be administered cautiously to patients suspected of having pheochromocytoma or insulinoma.
Secondary hypoglycemia may occur and should be countered by adequate carbohydrate intake following glucagon treatment.
Glucagon may release catecholamines from pheochromocytomas and is contraindicated in patients with this condition.
Allergic reactions may occur and include generalized rash, and in rare cases anaphylactic shock with breathing difficulties, and hypotension. The anaphylactic reactions have generally occurred in association with endoscopic examination during which patients often received other agents including contrast media and local anesthetics. The patients should be given standard treatment for anaphylaxis including an injection of epinephrine if they encounter respiratory difficulties after GlucaGen® injection.

## PRECAUTIONS

*General*-In order for GlucaGen® treatment to reverse hypoglycemia, adequate amounts of glucose must be stored in the liver (as glycogen). Therefore, GlucaGen® should be used with caution in patients with conditions such as prolonged fasting, starvation, adrenal insufficiency or chronic hypoglycemia because these conditions result in low levels of releasable glucose in the liver and an inadequate reversal of hypoglycemia by GlucaGen® treatment. Caution should be observed when glucagon is used in diabetic patients or in elderly patients with known cardiac disease to inhibit gastrointestinal motility.

*Information for Patients*-Refer patients and family members to the Information for Patients for instructions describing the method of preparing and injecting GlucaGen®. Advise the patient and family members to become familiar with the technique of preparing glucagon before an emergency arises. Instruct patients to use 1 mg for adults or ½ the adult dose (0.5 mg) for children weighing less than 55 lb (25 kg). To prevent severe hypoglycemia, patients and family members should be informed of the symptoms of mild hypoglycemia and how to treat it appropriately. Family members should be informed to arouse the patient as quickly as possible because prolonged hypoglycemia may result in damage to the central nervous system. Patients should be advised to inform their physician when hypoglycemic reactions occur so that the treatment regimen may be adjusted if necessary.

*Laboratory Tests*-Blood glucose measurements may be considered to monitor the patient's response.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*-Long term studies in animals to evaluate carcinogenic potential have not been performed. Several studies have been conducted to evaluate the mutagenic potential of glucagon. The mutagenic potential tested in the Ames and human lymphocyte assays, was borderline positive under certain conditions for both glucagon (pancreatic) and glucagon (rDNA) origin. *In vivo*, very high doses (100 and 200 mg/kg) of glucagon (both origins) gave a slightly higher incidence of micronucleus formation in male mice but there was no effect in females. The weight of evidence indicates that GlucaGen® is not different from glucagon pancreatic origin and does not pose a genotoxic risk to humans.

GlucaGen® was not tested in animal fertility studies. Studies in rats have shown that pancreatic glucagon does not cause impaired fertility.[1]

*Pregnancy-Pregnancy Category B*-Reproduction studies were performed in rats and rabbits at 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 $mg/m^2$ for rats and rabbits, respectively, and revealed no evidence of 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.

*Nursing Mothers*-It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GlucaGen® is administered to a nursing woman.

No clinical studies have been performed in nursing mothers, however, GlucaGen® is a peptide and intact glucagon is not absorbed from the GI tract. Therefore, even if the infant ingested glucagon it would be unlikely to have any effect on the infant. Additionally, GlucaGen® has a short plasma half-life thus limiting amounts available to the child.

*Pediatric Use*-For the treatment of hypoglycemia: The use of glucagon in pediatric patients has been reported to be safe and effective.[2,3,4,5]

For use as a diagnostic aid: Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

Severe side effects are very rare, although nausea and vomiting may occur occasionally especially with doses above 1 mg or with rapid injection (less than 1 minute).[1] Hypotension has been reported up to 2 hours after administration in patients receiving GlucaGen® as premedication for upper GI endoscopy procedures. Glucagon exerts positive inotropic and chronotropic effect and may therefore cause tachycardia and hypertension. Adverse reactions indicating toxicity of GlucaGen® have not been reported. A transient increase in both blood pressure and pulse rate may occur following the administration of glucagon. Patients taking ß-blockers might be expected to have a greater increase in both pulse and blood pressure, an increase of which will be transient because of glucagon's short half-life. The increase in blood pressure and pulse rate may require therapy in patients with pheochromocytoma or coronary artery disease. (see OVERDOSAGE).

Allergic reactions may occur in rare cases. (see WARNINGS).

## OVERDOSAGE

*Signs and Symptoms*-No reports of overdosage with GlucaGen® have been reported. It is expected, if overdosage occurred, that the patient may experience nausea, vomiting, inhibition of GI tract motility, increase in blood pressure and pulse rate.[1] In case of suspected overdosing, the serum potassium may decrease and should be monitored and corrected if needed.

The IV and SC $LD_{50}$ for GlucaGen® in rats and mice ranges from 100 to greater than 200 mg/kg body weight.

*Treatment*-Standard symptomatic treatment may be undertaken if overdosage occurs. If the patient develops a dramatic increase in blood pressure, 5 to 10 mg of phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed. It is unknown whether GlucaGen® is dialyzable, but such a procedure is unlikely to provide any benefit given the short half-life and nature of the symptoms of overdose.

## DOSAGE AND ADMINISTRATION

GlucaGen® should be reconstituted with the supplied 1 ml of Sterile Water for Reconstitution (if supplied) or 1 ml Sterile Water for Injection, USP.

Using the syringe, withdraw all of the Sterile Water for Reconstitution (if supplied) or 1 ml Sterile Water for Injection, USP and inject into the GlucaGen® vial. Roll the vial gently until powder is completely dissolved and no particles remain in the fluid. The reconstituted fluid should be clear and of water-like consistency. The reconstituted GlucaGen® gives a concentration of approximately 1 mg/ml glucagon. The reconstituted GlucaGen® should be used immediately after reconstitution. Discard any unused portion.

*For the treatment of hypoglycemia*: For adults and for pediatric patients weighing 55 lb (25 kg) or more, administer 1 mg by subcutaneous, intramuscular, or intravenous injection.[1,6] According to the literature, ½ adult dose (0.5 mg) is recommended for pediatric patients weighing less than 55 lb (25 kg) or younger than 6-8 years old.[2,3,4,5,6]

Emergency assistance should be sought if the patient fails to respond within 15 minutes after subcutaneous or intramuscular injection of glucagon. The glucagon injection may be repeated while waiting for emergency assistance.[1] Intravenous glucose MUST be administered if the patient fails to respond to glucagon. When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent recurrence of hypoglycemia.

*Directions for Use as a Diagnostic Aid:* Reconstitute as indicated above. Discard any unused portion. When the diagnostic procedure is over, give oral carbohydrate to restore the liver glycogen and prevent occurrence of secondary hypoglycemia.

**Time of maximal glucose concentration**
Intravenous: 5 to 20 minutes
Intramuscular: 30 minutes
Subcutaneous: 30 to 45 minutes

**Time for GI smooth muscle relaxation**[1]
Intravenous: 0.25 to 2 mg (IU) - 45 seconds
Intramuscular:
1 mg (IU) - 8 to 10 minutes
2 mg (IU) - 4 to 7 minutes

**Duration of action -**
Hyperglycemic action - 60 to 90 minutes
Smooth muscle relaxation -[1]
Intravenous:
0.25 to 0.5 mg (IU) - 9 to 17 minutes
2 mg (IU) - 22 to 25 minutes
Intramuscular:
1 mg (IU) - 12 to 27 minutes
2 mg (IU) - 21 to 32 minutes

## STABILITY AND STORAGE

*Before Reconstitution*: The GlucaGen® package may be stored up to 24 months at controlled room temperature 20° to 25° C (68° to 77° F) prior to reconstitution. Avoid freezing and protect from light. GlucaGen® should not be used after the expiry date on the vials.

*After Reconstitution*: Reconstituted GlucaGen® should be used immediately. Discard any unused portion. If the solution shows any sign of gel formation or particles, it should be discarded.

**HOW SUPPLIED**
GlucaGen® Diagnostic Kit includes:
1 vial containing 1 mg (1 IU) GlucaGen® [glucagon (rDNA origin) for injection]
1 vial containing 1ml Sterile Water for Reconstitution
NDC 55390-004-01
OR
The GlucaGen® 10-pack includes:
10x1 vial containing 1 mg (1 IU) GlucaGen® [glucagon (rDNA origin) for injection]
NDC 55390-004-10

Edition August 2003

**REFERENCES:**

1. *Drug Information for the Health Care Professional.* 17th ed. Rockville, Maryland: The United States Pharmacopeial Convention, Inc; 1997; Vol. 1, IA: 1516-1518.
2. Gibbs et al: Use of Glucagon to terminate insulin reactions in diabetic children. *Nebr Med J* 1958;43:56-57.
3. Carson MJ, Koch R, Clinical studies with glucagon in children. *J Pediatr* 1955; 47:161-170.
4. Shipp JC, et al: Treatment of insulin hypoglycemia in diabetic campers. *Diabetes* 1964; 13:645-648.
5. Aman J, Wranne L: Hypoglycemia in childhood diabetes II: Effect of subcutaneous or intramuscular injection of different doses of glucagon. *Acta Pediatr Scand 1988; 77:548-553.*
6. Aynsley-Green AS, Eyre JA, and Soltesz G, Hypoglycaemia in diabetic children. In: Frier BM and Fisher BM, eds *Hypoglycaemia and Diabetes*, Edward Arnold, 1993; 237-238.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-918/S-003**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

**Division of Metabolic and Endocrine Drug Products**

# CONSUMER SAFETY OFFICER REVIEW

**Application Number:** NDA 20-918/S-003

**Name of Drug:** GlucaGen (glucagon [rDNA origin] for injection)

**Sponsor:** Novo Nordisk

**Material Reviewed:** Package insert (Edition March 2001), Final Printed Labeling
Carton Label, Final Printed Labeling

**Submission Date:** July 19, 2001
**Receipt Date:** July 20, 2001

## Background and Summary

NDA 20-918 GlucaGen (glucagon [rDNA origin] for injection) was approved on June 22, 1998, for the following indications:

1. Treatment of hypoglycemia.
2. Use as a diagnostic aid during radiological examination to temporarily inhibit movement of the gastrointestinal tract.

This supplement (S-003) was submitted as a Changes Being Effected supplement on July 19, 2001. The S-003 provides for the following changes:

1. INDICATIONS AND USAGE:
   Addition of the following sentence "Because GlucaGen depletes glycogen stores, the patient should be given oral carbohydrates as soon as the procedure is completed." at the end of this section.

2. DOSAGE AND ADMINISTRATION:
   Addition of "When the diagnostic procedure is over, give oral carbohydrates to restore the liver glycogen and prevent occurrence of secondary hypoglycemia." at the end of this section.

## Review

This supplement (S-003) proposed insert is compared to the approved PI for Supplement 001 (Edition Date: July 1999) and Supplement 002 (Edition Date: July 1999) and found it to be identical except for the following changes:

I. Package insert:

1. Other Ingredients subsection:

   The sponsor has added ". . . (if supplied) or with Sterile Water for Injection, USP, . . . " after ". . . Sterile Water for Reconstitution".

   This change was approved under S-002 and, therefore, it is acceptable.

2. Indication and Usage section:

   The following sentence "Because GlucaGen depletes glycogen stores, the patient should be given oral carbohydrates as soon as the procedure is completed." is added at the end of this section.

   The medical officer, Dr. Robert Misbin, agrees with the proposed addition.

3. Dosage and Administration section:

   i. The sponsor has added ". . . (if supplied) or with Sterile Water for Injection, USP, . . . " after ". . . Sterile Water for Reconstitution".

   This change was approved under S-002 and, therefore, it is acceptable.

   ii. The beginning of the second paragraph was changed from "Draw up all of the Sterile Water for Reconstitution with syringe and inject into the GlucaGen vial." to "Using the syringe, withdraw all of the Sterile Water for Reconstitution (if supplied) or 1 ml Sterile Water for Injection, USP and inject into the GlucaGen vial."

   This change was approved under S-002 and, therefore, it is acceptable.

iii. Addition of "When the diagnostic procedure is over, give oral carbohydrates to restore the liver glycogen and prevent occurrence of secondary hypoglycemia."at the end of this section.

The proposed addition is acceptable to the medical officer, Dr. Robert Misbin.

4. Stability and Storage subsection:

Storage condition prior to reconstitution is changed from the GlucaGen package should be kept refrigerated until the expiration date or stored up to 12 months at room temperature prior to reconstitution to the GlucaGen package may be stored up to 24 months at controlled room temperature prior to reconstitution.

This change was approved under S-001 and, therefore, it is acceptable.

5. How Supplied section:

Added the GlucaGen 10-vial pack marketing presentation.

This change was approved under S-002 and, therefore, it is acceptable.

II. Carton Label:

i. Storage temperature is changed from 2°- 8°C (36°F-46°F) to 20°C-25°C (68°F-77°F).

This change is acceptable since it reflects the storage condition on the package insert. Storage condition change was approved under S-001 and, therefore, it is acceptable.

ii. The statement "For hospital use only" was approved under S-002. However, that statement is changed to "For Institutional Use Only" and the statement is bolded in S-003.

## Conclusions

The proposed package insert is acceptable for an approval.

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/s/

Julie Rhee
7/11/02 04:51:14 PM
CSO

| **RECORD OF TELEPHONE CONVERSATION/MEETING** | **Date:** July 24, 2001 |
|---|---|
| Re: 7/19/01 submission (SLR-003)<br><br>Background: The 7/19/01 submission is a CBE supplement which provides for a change in the Dosage and Administration section of the PI. The cover letter states that the change was made March 2001.<br>**********<br><br>I called Dr. Tan to ask why this supplement was not submitted when the change was made in March 2001. She replied that March 2001 is when they made the change internally for the printing purpose; however, they did not implement the change until recently. I asked for the implementation date but she could not provide it and said she'll get back to me with the date. I asked Dr. Tan that in the future they include an implementation date on the cover letter and they should submit a supplement before they implement the change. She agreed to do so.<br><br>I also asked her to include 20 copies of FPL rather than 12 copies with CBE submission in the future. I also asked her to provide me a diskette or an e-mail attachment that includes the currently approved PI as well as the one with the proposed changes. She agreed to send a diskette. I asked her to include the implementation date for this supplement when she sends me the diskette. She agreed.<br><br>---<br>**Name: Julie Rhee** | **NDA#: 20-918**<br><br>**Telecon/Meeting initiated by:**<br><br>O FDA<br><br>**By:** Telephone<br><br>**Product Name:** GlucaGen® (glucagon [rDNA origin] for injection)<br><br>**Firm Name:** Novo Nordisk<br><br>**Name and Title of Person with whom conversation was held:** Elizabeth Tan, Ph.D. Assistant Director, Regulatory Affairs<br><br>**Phone:** (609) 987-5940 |

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/s/
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Julie Rhee
7/24/01 11:12:20 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-918/S-003

**CBE-0 SUPPLEMENT**

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

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

| | |
|---|---|
| Name of Drug Product: | GlucaGen® (glucagon [rDNA origin] for injection) |
| NDA Number: | 20-918 |
| Supplement Number: | S-003 |
| Date of Supplement: | July 19, 2001 |
| Date of Receipt: | July 20, 2001 |

This supplemental application, submitted as a "Supplement - Changes Being Effected" supplement, proposes to add a statement in the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the package insert that a patient should be given oral carbohydrates as soon as the diagnostic procedure is completed to prevent occurrence of secondary hypoglycemia.

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 September 18, 2001, in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6424.

Sincerely,

*{See appended electronic signature page}*

Julie Rhee
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/
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Julie Rhee
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