CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201849Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA – 505 (b) (2)
Application Number(s)	201-849
Priority or Standard	Standard
Submit Date(s)	August 8, 2014
Received Date(s)	August 8, 2014
PDUFA Goal Date	May 8, 2015
Division / Office	Division of Metabolism and Endocrinology Products/ Office of New Drugs
Reviewer Name(s)	Giovanni Cizza, M.D., Ph.D., MHSc.
Review Completion Date	March 30, 2015
Established Name	Glucagon for Injection
(Proposed) Trade Name	Not applicable
Therapeutic Class	Gastrointestinal motility inhibitor
Applicant	Fresenius Kabi USA, LLC
Dosage forms/Strength	Sterile lyophilized power for injection (1 mg per vial)
Indication(s)	For use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract
Intended Population(s)	Patients undergoing radiological examination of the gastrointestinal tract

Table of Contents

Table of Tables

Table of Figures

No table of figures entries found.

1 Recommendations/Risk Benefit Assessment

This document contains the clinical review for Glucagon for Injection, NDA 201-849.

This submission is a 505 (b) (2) second cycle application which relies on the Agency's previous finding of safety and effectiveness for the listed drug, GlucaGen (NDA 20-918, held by Novo Nordisk, and distributed by Bedford Laboratories). GlucaGen is approved for administration by subcutaneous (SC), IM or IV for the following indications: a) emergency use for treatment in severe hypoglycemia; b) as a diagnostic aid during radiologic examinations to temporarily inhibit gastrointestinal motility.

The Applicant is seeking approval as a diagnostic aid for use during radiological examination to temporarily inhibit movement of the gastrointestinal tract (administration by IM and IV routes). This application consists of a relative bioavailability study comparing the pharmacokinetics/pharmacodynamics of the proposed Glucagon for Injection to the Listed Drug following SC administration.

1.1 Recommendation on Regulatory Action

This is a 505 (b)(2) application referencing GlucaGen, and the Applicant needed to demonstrate that Glucagon for Injection is bioequivalent to GlucaGen. According to his review of the submitted data, this reviewer recommends the approval of Glucagon for Injection as a diagnostic aid for use as a gastrointestinal motility inhibitor. The reviewer's recommendation to approve Glucagon for Injection is based on FDA's findings of safety and effectiveness for the listed drug and data demonstrating bioequivalence, according to the regulatory requirements for a 505 (b)(2) application.

1.2 Risk Benefit Assessment

The overall tolerability and risk/benefit balance favor approval of Glucagon for Injection as a diagnostic aid for use during radiological examination to temporarily inhibit movement of the gastrointestinal tract. For this 505 (b)(2) application some of the information required for approval, including information on safety and tolerability, comes from previous studies not conducted by the Sponsor. Furthermore, according to the review of the clinical data produced by the Sponsor, no specific safety issues were identified when comparing Glucagon for Injection to the Listed Drug. The AEs reported were expected and resolved spontaneously in a short period of time. The study did demonstrate bioequivalence for both the PK and the PD parameters.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

The established name for the product under consideration is Glucagon for Injection. No trade name has been proposed by the Applicant. Glucagon belongs to the chemical class of protein, and to the pharmacological class of anti-hypoglycemic. The Applicant's proposed indication for Glucagon for Injection is for use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.

Glucagon is a naturally occurring peptide hormone consisting of 29 amino acids that is secreted by the alpha cells of the pancreas. Glucagon acts on the liver to increase glucose production via glycogenolysis and gluconeogenesis, thereby effectively countering the effects of insulin. In addition, glucagon has inhibitory effects on the motility of the gastrointestinal tract.

The Listed Drug, GlucaGen 1 mg (1 IU) is supplied as a sterile, lyophilized white powder in a glass vial alone, or accompanied by Sterile Water for Reconstitution (1 mL) also in a glass vial.

2.2 Tables of Currently Available Treatments for Proposed Indications

Two glucagon products—both produced from recombinant DNA expression and identical in amino acid sequence to the native peptide—are currently approved in the United States as a diagnostic aid to temporarily inhibit gastrointestinal motility. One of these is GlucaGen which is the Listed Drug for this 505(b)(2) application. GlucaGen was approved on 6/22/98 (NDA 20-918). GlucaGen is dosed subcutaneously, intramuscularly, or intravenously. Eli Lilly's glucagon for injection (no proprietary name) was approved on 9/11/98 (NDA 20-928). Both of these glucagon products are also indicated for the treatment of severe hypoglycemia in patients with diabetes mellitus (see 2.3 below).

2.3 Availability of Proposed Active Ingredients in the United States

The active ingredient in the Applicant's proposed Glucagon for Injection is glucagon. Two glucagon products are available in the US, the Listed Drug by Novo Nordisk and Lilly's Glucagon for Injection, as noted above. GlucaGen is currently available in a Glucagon Emergency Kit that also contains as delivery system prefilled syringes. Lilly's Glucagon for injection comes also in a similar preparation. The Applicant's Glucagon for Injection is not provided with a kit, which makes it unsuitable for emergency use for the treatment of severe hypoglycemia.

2.4 Important Safety Issues with Consideration to Related Drugs

Glucagon is contraindicated in patients with pheochromocytoma or insulinoma, since administration of glucagon may stimulate excessive release of catecholamines or insulin, which may result in significant increase in blood pressure or in hypoglycemia, respectively. Glucagon is also contraindicated in patients with known hypersensitivity to glucagon or lactose.

Warnings and precautions for glucagon are listed for patients with diabetes, as glucagon may cause hyperglycemia; for patients with cardiac disease, as glucagon may increase myocardial oxygen demand, blood pressure, and pulse rate. Allergic reactions may occur and include generalized rash, and in rare cases anaphylactic shock with breathing difficulties, and hypotension. Adverse reactions include temporary increase in blood pressure and pulse, hypersensitivity and allergic reactions, nausea and vomiting.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The current submission is a second cycle resubmission for this NDA, as a Complete Response was issued for the original NDA.

On September 30, 2010, the Applicant submitted the original 505(b)(2) NDA, for Glucagon for Injection, which relied on the Agency's previous finding of safety and effectiveness for the Listed Drug, GlucaGen. No clinical safety/efficacy trials were conducted, as the decision on regulatory action was to be based on the results of the BE study.

On December 3, 2010 the Applicant was sent a Refuse-to-File letter, stating that the application was not "*sufficiently complete to permit a substantive review*". The Applicant's original application (b) (4) for use as a radiological diagnostic aid. (b) (4)

[redacted] (b) (4)

On March 3, 2011 a Type B was held (meeting category: Post Refuse to File Informal Conference). Listed below is a summary the Agency's requests and the Applicant's reply (in Italic):

- Data set for the BE study were not provided.
  The Applicant agreed to provide these datasets.

- The proposed commercial product did not include a complete emergency kit.
  The Applicant clarified that [redacted] (b) (4) *the only indication they were pursuing was as a diagnostic aid within a healthcare/ professional administrative facility and for that indication no kit was necessary.*

- Provide PK dataset for glucagon and PD data for glucose for the BE study No. 20090101.
  The Applicant agreed to provide these datasets.

- Perform a separate BE study involving subcutaneous administration to support a clinical efficacy claim [redacted] (b) (4).
  The Applicant provided a literature based PK bridging argument, which was found acceptable by the Agency.

- Clarify why the Applicant stated that for BE analysis corrected glucagon data were used, whereas the primary PK comparison was instead based on non baseline corrected data.
  The Applicant clarified that this was a typographical error.

- Justify why the Applicant was planning to [redacted] (b) (4)
  The Applicant agreed to use non adjusted glucagon data.

On November 30, 2011 the Applicant resubmitted the 505(b)(2) NDA application. The Applicant sought an indication for Glucagon for Injection as a diagnostic aid for use as a gastrointestinal motility inhibitor. Glucagon for Injection was to be administered via the intravenous route. The Applicant noted the following:

In summary, and presented here-in, discussions, decisions and agreements made in the referenced RTF meeting between the Agency and APP Pharmaceuticals (APP) included:

1) *That a nonclinical bridge must be established between the APP Glucagon for Injection and the RLD, the Bedford GlucaGen®. APP has established this bridge through the definitive identification and the comparison of the impurity levels of the two products on stability.*

2) *APP* (b) (4) *not to pursue either the hypoglycemia indication or the subcutaneous route of administration; only the gastrointestinal indication via the intravenous route of administration is now being pursued by APP.*

On September 27, 2012, the Agency issued a Complete Response Letter. Clinical Pharmacology had concluded that the pivotal bioavailability study (200090101) was not acceptable, due to deficiencies in the bioanalytical assay for glucose. The glucose assay used by the Applicant was not compliant with 21 CFR 320.29 (a) and not consistent with the methodology recommended by Guidance for Industry: Bioanalytical Method Validation. Because the Applicant had not retained plasma samples for glucose reanalysis, a new BE study was required. On October 5, 2012 the Applicant requested a type A meeting which was granted by the Agency and scheduled for November 27, 2012. In this meeting: a) it was decided that both glucose and glucagon data had to be included in the BE study; b) the Applicant agreed to conduct a new BE study for only the subcutaneous indication. Previously, the Office of Compliance had rendered a "withhold" recommendation for deficiencies relating to the (b) (4) were noted in the Applicant facility in Grand Island, New York. For that reason the Applicant had subsequently decided to use a different facility, located in Melrose Park, IL.

On August 8, 2014 the Applicant resubmitted their NDA. This resubmission was considered a complete, class 2 response to the Agency's action letter dated September 27, 2012.

Table 1: Regulatory History for NDA 201-849, Glucagon for Injection

Date	Regulatory Action	Key comments
9/30/2010	Original NDA submitted by APP Pharmaceuticals	

12/3/2010	Refuse to file (RTF)	Nonclinical: Impurities above 1% limits were not qualified. [redacted] (b) (4)
3/11/2011	Meeting to discuss RTF	Literature based PK bridging not acceptable. As relative bioavailability (BA) between SC and IM differed for glucagon, [redacted] (b) (4)
11/30/2011	Resubmission after RTF	1 relative BA study (IM administration); [redacted] (b) (4)
9/27/2012	Complete Response (CR)	Bioanalytical assay for glucose not validated
11/27/2012	Meeting to discuss CR	Sponsor agreed to conduct a new study with glucagon administration via SC route
8/8/2014	Resubmission class 2	1 relative BA study; SC route; seeking only diagnostic aid indication.

Source: created by reviewer.

2.6 Other Relevant Background Information
None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the data submitted in this NDA were of sufficient quality and completeness to permit a substantive review. The Sponsor states that there were no recorded protocol deviations in the submitted study.

For the current submission, the Agency required the Applicant to recalculate concentrations of glucose for calibration standards, quality control samples, and study plasma samples for the assays in study AA98483-02 based on the audit by the Division of Bioequivalence and GLP Compliance (DBGLPC) (detailed reason described below). On December 19, 2014, a major amendment was received and the goal date was extended to May 8, 2015.

From October 23 to October 30, 2014, DBGLPC audited the clinical and analytical portions of Study GLUC-002-CP1. The conclusions of the audit were as follows:

- *The incomplete labeling of drug products from the two shipments of study drugs does not appear to have compromised the integrity of subject dosing (i.e., who got which product).*

- *The adjusted data for glucose concentrations in Amendment 1 to the bioanalytical final report for study AA98483-02, dated December 10, 2014, are acceptable for Agency review.*

- *The analytical data for glucagon concentrations in the original bioanalytical final report for study AA98483-01 dated October 31, 2013, are acceptable for Agency review.*

During the course of her review, Dr. Vaidyanathan, Clinical Pharmacology reviewer, identified in a case report form errors in the in batch information of products used and the route of administration. An information request was sent to the Applicant regarding the discrepancies. The Applicant responded that the information in the case report form was an error which they corrected subsequently. An inspection conducted by OSI verified the claim that was found to be acceptable (DARTTS report dated 1/5/2015).

3.2 Compliance with Good Clinical practices

The Sponsor states that the study addressed in this application were in accordance with the ethical principles set forward in the Declaration of Helsinki and Title 21 of the Code of Federal Regulations (ref. Module 5, protocol page 6).

3.3 Financial Disclosures

Based on review of Form 3454, the Applicant certified that neither the Principal Investigator nor the Sub-Investigator reported potential financial conflicts of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The primary review pertaining to Chemistry, Manufacturing, and Controls has been completed. No significant issues have been raised pertaining to this discipline. Below is an excerpt from the review of Dr. Muthukumar Ramaswawy. For more details please refer to Dr. Ramaswawy's review.

From quality perspective, the NDA is recommended for approval. This approval recommendation is based on the current and past CMC reviews (dated Aug.16, 2012) for this NDA application, a recommendation for approval from microbiology reviewer Dr. Metcalfe dated Aug. 5, 2012 as well acceptable recommendation from Office of Compliance for the manufacturing facilities associated with this NDA.

In addressing the deficiencies of the manufacturing facility noted by the Agency in the Complete Response Letter dated 09/27/2012, the Applicant stated in the resubmission dated August 8, 2014:

FK USA is (b) (4) *(manufactured at FK USA's Grand Island, NY facility) with the NDA 201849 Glucagon for Injection (SEQ 0018) vials of glucagon drug product.*

4.2 Clinical Microbiology

For the current application, no clinical microbiology review was required. The microbiology review from the first cycle was sufficient (see 4.1).

4.3 Nonclinical Pharmacology/Toxicology

No new pharmacology studies were submitted with the current submission. Pharmacology studies were submitted with the original NDA, reviewed and found acceptable on 7/26/2012. These studies are briefly summarized below.

In a 28-day intramuscular (IM) toxicity study in rats, doses of 0, 1, and 5 mg/kg/day of the drug product were administered to rats. A group of rats was administered GlucaGen (5 mg/kg/day) for comparison. A NOAEL of <5 mg/kg/day was estimated. This NOAEL would provide a safety margin of <24 X in human subjects based on body surface area. No actual NOAEL could be established as histopathology findings were noted in one sex (e.g. heart findings in female rats: kidney findings in male rats),

following daily repeated treatment in euglycemic healthy rats. In addition, 2 two genotoxicity studies (Ames and chromosomal aberration assay) comparing glucagon to GlucaGen were submitted. No positive mutagenic responses were noted in the Ames assay (i.e. the assay was negative). The chromosomal aberration test was also negative.

On 12/9/2014, the primary review pertaining to preclinical pharmacology/toxicology for the current review cycle was completed. The pharmacology/toxicology reviewer, Dr. Indra Antoniplillai identified no outstanding pharmacology/toxicology and recommended approval pending labeling changes. The labeling changes recommended by Dr. Antoniplillai are noted below in bold:

Reviewer's recommended changes:
8.1 Pregnancy

Pregnancy Category B. Reproduction studies were performed in rats and rabbits at **GlucaGen (recombinant)** doses of 0.4, 2, 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. Glucagon does not cross the human placenta barrier.

Reviewer's recommended changes:
8.1 Pregnancy

Pregnancy Category B. Reproduction studies were performed in rats and rabbits at **GlucaGen (recombinant)** doses of 0.4, 2, 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. Glucagon does not cross the human placenta barrier.

(b) (4)

Justificationforthechanges: (b) (4)

Source: Pharmacology/Toxicology Review and Evaluation, memo dated 12/9/201 from Dr. Antonipillai.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Glucagon promotes hepatic glucose production via gluconeogenesis and glycogenolysis by stimulating adenylate cyclase to increase cyclic adenosine monophosphate (cAMP). This increased cAMP activates a series of enzymatic activities, leading to increased plasma glucose. Extra hepatic effects of glucagon include relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon.

4.4.2 Pharmacodynamics

The only clinical study conducted in support of this NDA was a clinical pharmacology study GLUC-002-CP to demonstrate BE of Glucagon for Injection with GlucaGen. The pharmacodynamics findings of this study are described in section 6.

4.4.3 Pharmacokinetics

The pharmacokinetic findings of study GLUC-002-CP are described in section 6.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There was only one clinical study submitted to the NDA, Study Gluc-002-CP1: the pivotal bioavailability/bioequivalence entitled: “Bioequivalence of a Test Formulation of Glucagon for SC Injection Compared to Glucagon for Injection (Bedford Laboratories) Under Fasted Conditions” as shown in Table 2.

Table 2: Study Gluc-002-CP1

Type of Study	**Study ID**	**Objective(s) of the Study**	**Study Design**	**Subjects**
BE	Gluc-002-CP (Repeated Study)	To ascertain the PK and PD bioequivalence of an SC injection of 1 mg (1 IU) of Glucagon for Injection in comparison to the Listed Drug, GlucaGen, 1 mg (1 IU), administered SC in healthy adult subjects.	A single center, randomized, open label, four way cross-over study. Study periods were separated by at least a seven-day interval.	12 M/20F Healthy volunteers

Source: created by reviewer. BE=bioequivalence; SC=subcutaneously

5.2 Review Strategy

This reviewer reviewed study Gluc-002-CP1 (see Table 2) focusing predominantly on safety findings. The PK and PD results from this study were reviewed in greater depth by Dr. Jayabharathi Vaidyanathan, Clinical Pharmacology reviewer. Please refer to her review for an in-depth discussion of the PK and PD data.

5.3 Discussion of Individual Studies/Clinical Trials

Study Phase and Dates Conducted: Phase 1 (BE) study initiated on May 4, 2013. Last subject's last visit/contact, June 9, 2013.

Objectives:

- To ascertain the pharmacodynamics and pharmacokinetics bioequivalence of a SC injection of 1 mg (1 IU) of Glucagon for Injection in comparison to GlucaGen (Listed Drug), 1 mg (1 IU), SC in healthy adult subjects.

- To compare the safety of Glucagon for Injection with the Listed Drug.

Study Design: Single-center, randomized, open-label, two-treatment, four-period, replicate crossover study.

Main Inclusion/Exclusion Criteria: Healthy males or women 18 years old or older with a BMI of 18 to 30 kg/m^2 inclusive, without any significant medical or laboratory findings. No use of any drugs known to induce or inhibit hepatic drug metabolism.

Treatments: A single dose of 1 mg (1 IU) of Glucagon for Injection or a single dose of 1 mg (1 IU) Listed Drug, via SC injection.

Study Site including Enrollment: 32 healthy subjects randomized at 1 study site in the US.

Efficacy Assessments:

Primary endpoints: Baseline corrected PK (glucagon AUC and C_{max}) and PD (glucose AUC and BG_{max}) parameters.

Secondary endpoints: Uncorrected PK (glucagon AUC and C_{max}) and PD (glucose AUC and BG_{max}) parameters.

Safety Assessments: AE monitoring, clinical laboratory tests (hematology and chemistry) vital signs, physical examination, 12-lead ECG, concomitant medications, bedside glucose measurements. Monitoring of the injection site reactions at 30 minutes, 2 and 4 hours post-dose

Study procedures: Subjects were screened within 2 weeks before the first study drug administration, and if eligible, admitted to the clinic on Day One for the first study period, Period One. The study comprised of four periods: Period One through Period Four. Subjects were randomized in a one: one ratio to receive in each period either a single dose of Glucagon for Injection or a single dose of the Listed Drug via SC injection. Venous blood samples for the PK assay (glucagon) and the PD assay (glucose) were collected 3 times (2, 1, and 0 hour) before study drugs injections and 14 times (5, 10, 15, 20, 25, 30, 40, 50 minutes, and at 1, 1.5, 2, 2.5, 3, and 4 hours) after injections. The study was conducted in 2 groups of equal number and treated on different days.

PK & PD population: subjects who completed the four study periods.

Safety population: subjects who received at least one dose of study drug.

6 Review of Efficacy

Efficacy Summary

For the current application, the Applicant intends to rely on FDA's previous findings of safety and effectiveness for the listed drug GlucaGen. The objective of study Gluc-002-CP1 was to establish the BE of Glucagon for Injection to GlucaGen (Listed Drug).

Results indicate that the synthetic glucagon product met the PK criteria (baseline uncorrected glucagon pharmacokinetic PK parameters). In addition, the glucose (pharmacodynamic, PD; baseline corrected glucose) parameters met the PD criteria.

Please refer to Section 7 of this review for a discussion of the safety findings from the single pivotal BE study, Study Gluc-002-CP1.

6.1 Indication

The proposed indication sought by the applicant is "for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract".

6.1.1 Methods

As a 505(b) (2) application, the Applicant conducted the single, clinical pharmacology BE study Gluc-002-CP1 of Glucagon for Injection and the Listed Drug GlucaGen. I reviewed the results of study Gluc-002-CP1.

6.1.2 Demographics

The subjects enrolled in this BE study were healthy volunteers. The demographic and baseline characteristics at screening of all (N=32) randomized subjects are summarized in the table below.

Table 3 : Demographic Characteristics

Trait	**Results**
Sex	
Female	20 (62.5%)
Male	12 (37.5%)
Race	
American Indian or Alaska Native	10 (31.3%)
Black	1 (3.1%)
White	21 (65.6%)
Ethnicity	
Hispanic or Latino	32 (100%)
Age	42.6±9.75
Weight	157.58±22.29
BMI	26.75±2.43

Source: Created by reviewer based on Table 14.1.4, CSR.

The population consisted of 12 (37.5%) male and 20 (62.5%) female healthy subjects. Approximately 2/3 of subjects were women. In terms of race, the majority of subjects (65.6%) were White, approximately 1/3 of the subjects were of American Indian or of Alaska Native Latino race, and one subject was Black. In terms of ethnicity, 100% of subjects were Hispanic or Latino. Mean age was 42.6, age ranged from 25 to 66, mean BMI 26.7 kg/m^2 and BMI ranged from 21 to 30 kg/m^2.

6.1.3 Subject Disposition

A total of 32 subjects were randomized to treatment and a total of 27 subjects completed Study Gluc-002-CP1. One subject (#10) was discontinued after dosing (GlucaGen) in Period One due to AEs of elevated alanine aminotransferase (ALT) and elevated aspartate transaminase (AST) that however occurred prior to dosing (Day -One of Period One). Subjects 5, 9, 28, and 31 voluntarily withdrew consent for study participation after Period One; these four subjects had all received Glucagon for Injection. Table reports on the demographic features of the 4 subjects who withdrew voluntarily from Study Gluc-002-CP1.

Table 4: Clinical Features of Subjects who Discontinued Voluntarily from the Study

Subject Identification Number	Drug at time of discontinuation	Study Periods completed	Age, race, sex,
5	Glucagon for injection	One	64, white, female
9	Glucagon for injection	One	40, white, female
28	Glucagon for injection	One	33, white, female
31	Glucagon for injection	One	42, white, female

Source: created by reviewer based on information provided in the CSR.

Of the 4 subjects who completed only Period One, all subjects were white females, age ranging from 33 to 64, and 3 of the 4 subjects were on Glucagon for Injection. These subjects are further described in section 7.3.3.

Reviewer's note: The findings that all 4 subjects who voluntarily withdrew had received Glucagon for Injection and that all 4 subjects who voluntarily withdrew were females are of difficult interpretation and unclear significance, due to the small sample size.

6.1.4 Analysis of Primary Endpoint(s)

Primary PK Endpoints: Glucagon AUC and C_{max}

The analysis below is from the Office of Clinical Pharmacology which decided to conduct the primary PK analysis based on uncorrected values of glucagon, rather than on corrected glucagon values (Table 5). The primary PK endpoints selected by the Applicant were the baseline adjusted glucagon C_{max}, the baseline adjusted glucagon AUC_{0-t} and the baseline adjusted glucagon $AUC_{0-\infty}$. Results indicate that Glucagon for Injection met the bioequivalence criteria for the glucagon AUC_{inf} and C_{max} parameters (baseline uncorrected glucagon pharmacokinetic PK parameters) (Table 1).

For a detailed explanation of the Agency's approach and interpretation of results, please see the corresponding review from Clinical Pharmacology.

Table 5: Statistical comparison of the PK parameters of Glucagon for Injection and GlucaGen (baseline uncorrected) following SC administration

Parameter	Test LS Means	Reference LS Means	Ratio	90% CI
Cmax (pg/mL)	3532.87	3308.96	106.77	94.05 – 121.20
AUC0-t (pg.h/mL)	3019.96	2462.14	122.66	111.38 – 135.07
AUCinf (pg.h/mL)	3071.92	2759.31	111.33	102.14 – 121.35

Source: adapted from the Office of Clinical Pharmacology Review, Table 1.
t = 4 hours.

Primary PD Endpoints: Glucose AUC and C_{max}

The primary PD endpoints used were baseline corrected glucose Cmax, AUC0-2, and AUC0-4. These glucose parameters met the bioequivalence (BE) criteria (see table below). The baseline corrected glucose parameters met the BE criteria. Based on the results of this study, the recommended dosing information from the Listed Drug will be used for labeling of dosing information for Glucagon for Injection.

Table 6: Statistical comparison of baseline corrected glucose parameters for Glucagon for Injection and GlucaGen following SC administration

Parameter	Least-Square Means		Ratio	90% Confidence Intervals	
	Test	Reference		Lower CI	Upper CI
Cmax	941.47	991.65	94.94	86.22	104.54
AUC0-2	921.54	927.54	99.35	85.64	115.26
AUC0-4	979.16	958.87	102.12	88.04	118.45

Source: adapted from the Office of Clinical Pharmacology Review, Table 2.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints included the unadjusted PK (C_{max} and glucagon AUC) and the unadjusted PD (glucose AUC and C_{max}). The unadjusted PK (C_{max} and glucagon AUC) data from the current submission did not meet the BE criterion. However, as indicated in

the Clinical Pharmacology Review, in the previous submission the Applicant had shown BE for this end-point with the IM route of administration:

Additional supportive information comes from the PK data from the previous submission containing the bioequivalence study conducted for the proposed synthetic glucagon product as compared to the reference product following IM administration. As shown in the clinical pharmacology review (dated 8/27/2012 in DARRTS), the glucagon PK parameters met BE criteria following IM administration.
Source: from the Clinical Pharmacology Review.

6.1.6 Other Endpoints

No other endpoints were specified.

6.1.7 Subpopulations

Not assessed.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The BE study, Gluc-002-CP, studied 1 mg given SC to establish the BE between Glucagon for Injection and the Listed Drug. Based on the results of this study, the recommended dosing information from the Listed Drug will be used for labeling of dosing information for Glucagon for Injection.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

The BE study Gluc-002-CP1 involved 32 healthy volunteers and was largely unremarkable from a safety perspective. No deaths or SAEs were reported in this study.

Of the 32 subjects enrolled in this study, 31 subjects reported a total of 185 AEs after receiving at least one dose of study product. A similar number of subjects experienced AEs following either Glucagon for Injection or GlucaGen (31 vs. 29 subjects, respectively). In addition, the number of AEs was well-balanced between Glucagon for Injection and GlucaGen (96 vs. 89 AEs, respectively).

Overall, the most commonly reported AEs were injection site swelling, injection site redness, vomiting, nausea, asthenia, decreased blood pressure, and headache In general, no clinically meaningful changes were observed in clinical laboratory parameters or vital signs.

Of note, following the administration of GlucaGen, there was one severe AE of decreased blood pressure. This event was self-limited and resolved promptly without the need for medical intervention (see Section 7.3.4 for details).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study Gluc-002-CP was reviewed to evaluate the overall safety of Glucagon for Injection. The safety pool included all 32 enrolled subjects.

7.1.2 Categorization of Adverse Events

The AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) Version 16.0. Upon reviewing the coding of the verbatim terms to the preferred terms in the AE database submitted by the Applicant, it was determined that the verbatim terms were appropriately mapped to the correct preferred terms.

7.1.3 Pooling of data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All 32 subjects who were randomized to Study Gluc-002-CP1 received at least one dose of study drug. The overall demographic information for participants is provided in Table 1.

7.2.2 Exploration for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The routine clinical testing performed (described in the study methodology) included assessments of chemistry, liver, and hematology parameters and appeared adequate.

7.2.5 Metabolic, Clearance and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As per FDA EPC Established Pharmacological Class (page 39) the pharmacological class of antihypoglycemic contains only glucagon.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported.

7.3.2 Nonfatal Serious Adverse Events

No SAEs were reported.

7.3.3 Dropouts and/or Discontinuations

Of the 32 enrolled subjects, 27 subjects (approximately 85%) completed the study by participating in each of the four study periods.

A total of five subjects did not complete this study. One subject was excluded in Period One after receiving GlucaGen, due to elevated LFTs present prior to dosing. Four subjects withdrew consent after taking Glucagon for Injection, three subjects after Period One and one subject after Period Two. According to the Applicant each one of these four subjects withdrew consent voluntarily. However, upon closer evaluation of the individual case report forms of these four subjects, this reviewer noted that each of the four subjects who voluntarily withdrew after having received Glucagon for Injection had experienced one or more AEs prior to study withdrawal (Table 7).

Table 7: Adverse Events Reported in Subjects who Voluntarily Withdrew Consent.

Subject identification number	**Study period completed; treatment assignment**	**AEs prior to discontinuation**
5	Period Two (A)	Period Two: **Injection site redness** (<10 mm), lasted approximately 3.5 hours, spontaneous resolution
9	Period One (A)	Period One: **Low blood pressure** (90/65 mmHg) mild, lasted 20 minutes, spontaneous resolution (100/70 mmHg) **Vomiting** moderate, lasted 20 minutes, spontaneous resolution (supporting action) **Injection site redness** (10-20 mm), lasted approximately five hours, spontaneous resolution **Injection site swelling** (10-20 mm), lasted approximately five hours, spontaneous resolution **Hematoma and pain in the arm,** moderate, lasted approximately five hours, spontaneous resolution
28	Period One (A)	Period One: **Injection site redness,**(<10 mm)**,** lasted approximately four hours, spontaneous resolution **Injection site swelling,** (10-20 mm)**,** duration not listed, no resolution listed
31	Period One (A)	Period One: **Vomiting** x four, moderate,

		lasted 15 minutes, spontaneous resolution **Decreased blood pressure, (**95/70 mmHg;) mild, lasted 15 minutes, spontaneous resolution 100/70 mmHg **Weakness** mild, lasted 15 minutes, spontaneous resolution **Nausea,** mild, lasted 15 minutes, spontaneous resolution **Injection site swelling,** (<10 mm), lasted approximately nine hours, spontaneous resolution

A= Glucagon for Injection
Source: created by reviewer based on individual case report forms.

Reviewer's note: Each of the four subjects described above had received one dose of Glucagon for Injection before "voluntarily" withdrawing consent. It is unknown if the adverse events contributed to the withdrawal of consent.

7.3.4 Significant Adverse Events

There were no significant AEs reported in this study. However, following administration of the Listed Drug, the Applicant reported one severe AE of decreased blood pressure. In this case, a 47-year-old man experienced an episode of low blood pressure (65/43 mmHg) approximately 40 minutes after dosing that was accompanied by pallor, syncope, and dizziness. The episode resolved spontaneously within 10 minutes without the need for medical intervention and without apparent clinical sequelae.

7.3.5 Submission Specific Primary Safety Concerns
Swelling and redness at the injection site were recorded before dosing, and at 30 minutes, two and four hours post dose for each study period. In approximately 22% of cases, injection of study medication resulted in swelling at the injection site. Most of the injection site reactions were categorized as mild in severity, defined by the Applicant as swelling score of one (i.e., diameter <10 mm). Six injections, five after Glucagon for Injection and one after GlucaGen, resulted in moderate swelling, defined as a swelling score of two (diameter 10-20 mm). By four hours, swelling from 21 injections (12 vs. 9 episodes, Glucagon for Injection vs. GlucaGen) was still present but in most of these cases it was mild (Table 5). Of these 21 episodes that did not resolve by four hours, 19 resolved prior to the next treatment period. The remaining two events took place in Period Four, and no follow-up was documented thereafter, as per study protocol (Table 8).

Table 8: Incidence of Injection-Site Swelling

	Time From Dosing							
	Predose		30 minutes		2 hours		4 hours	
Swelling Score*	A N=58	B N=56	A N=58	B N=56	A N=58	B N=56	A N=58	B N=56
	n %	n %	n %	n %	n %	n %	n %	n %
0	58 (100%)	56 (100%)	42 (72%)	41 (73%)	41 (71%)	39 (70%)	46 (79%)	47 (84%)
1	0 (0%)	0 (0%)	11 (19%)	14 (25%)	10 (17%)	15 (27%)	10 (17%)	8 (14%)
2	0 (0%)	0 (0%)	5 (9%)	1 (2%)	7 (12%)	2 (4%)	2 (3%)	1 (2%)
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Swelling Scores: 0 = None, 1 = < 10 mm in diameter, 2 = 10 – 20 mm in diameter, 3 = > 20 mm in diameter
Test Product A = 1 mg (1 IU/ml) Glucagon for Injection (Fresenius Kabi USA)
Test Product B = 1 mg (1 IU/ml) Glucagen® for Injection (Bedford Laboratories)
Source: Table 14.3.5.8

Source: from CSR, Table 14.3.5.8

In approximately 27% of the cases, injection of study drugs resulted in redness at the injection site. Most of these cases were however of mild degree (score one, redness diameter < 10 mm). Five injections, two after receiving Glucagon for Injection and three after receiving the Listed Drug, resulted in redness of moderate degree (score two, redness diameter 10-20 mm). By four hours, redness from 23 injections was still present but in most of these cases it had improved to mild (
Table 9). No injection-site swelling or injection-site redness of severe (>20 mm) degree were reported. Of the remaining 23 episodes that did not resolve by four hours, 20 events resolved prior to the next period, one resolved in five weeks. The two remaining events occurred in two subjects after taking the Listed Drug. Because these events occurred in Period Four no follow-up was documented thereafter, as per study protocol (
Table 9)

Table 9: Incidence of Injection Site Redness.

Redness Score*	Time From Dosing							
	Predose		30 minutes		2 hours		4 hours	
	A N=58	B N=56	A N=58	B N=56	A N=58	B N=56	A N=58	B N=56
	n %	n %	n %	n %	n %	n %	n %	n %
0	58 (100%)	56 (100%)	39 (67%)	34 (61%)	41 (71%)	34 (61%)	46 (79%)	45 (80%)
1	0 (0%)	0 (0%)	17 (29%)	19 (34%)	15 (26%)	18 (32%)	11 (19%)	10 (18%)
2	0 (0%)	0 (0%)	2 (3%)	3 (5%)	2 (3%)	4 (7%)	1 (2%)	1 (2%)
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

N = Total number of observations
N (%) = number
Redness Scores: 0 = None, 1 = < 10 mm in diameter, 2 = 10 – 20 mm in diameter, 3 = > 20 mm in diameter
Test Product A = 1 mg (1 IU/ml) Glucagon for Injection (Fresenius Kabi USA)
Test Product B = 1 mg (1 IU/ml) Glucagen® for Injection (Bedford Laboratories)
Source: Table 14.3.5.8

Source: From Table 14.3.5.8, CSR.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Almost every subject 31/32 (96.9%) experienced an AE. In terms of incidence by system organ class (SOC), the most common AEs occurred in the general disorders and administration site conditions 90.6%, followed in decreasing order of incidence by gastrointestinal disorders 53.1%, investigations 46.9%, nervous system disorders 40.6%, vascular disorders 21.9%, and skin and subcutaneous disorders 6.3%. The overall incidence of AEs was similar, 93.5% vs. 89.7%, between Glucagon for Injection and GlucaGen.

The incidence of AEs in each one of the SOCs was balanced between Glucagon for Injection and the Listed Drug. Specifically, the incidence for Glucagon for Injection vs. GlucaGen was as follows: general disorders and administration site conditions, 77.4% vs. 82.8%; gastrointestinal disorders, 48.4% vs. 37.9%; investigations, 32.3% vs. 27.6%; nervous system disorders, 29.0% vs. 20.7%; vascular disorders, 9.7% vs. 17.2%; skin and subcutaneous tissue disorders, 3.2% vs. 3.4%.

In terms of specific AEs terms, the most common terms reported were: injection site swelling 75.0% and injection site erythema 71.9%, followed by nausea 43.8% and vomiting 40.6%, blood pressure decrease 37.5%, asthenia 31.3%, pallor 21.9%, and dizziness 16%. When examining the relative incidence of Glucagon for Injection and GlucaGen for selected terms of particular clinical interest, nausea and vomiting were

reported with similar incidence for Glucagon for Injection compared to the Listed Drug: nausea, 32.3% vs.27.6, vomiting 35.5% vs.24.1%. Asthenia was reported slightly more often with Glucagon for Injection than with GlucaGen (22.6% vs.13.8%) (Table 10).

Reviewer's note: Overall the AE profile was similar between Glucagon for Injection and GlucaGen. Although asthenia appeared to be more common on Glucagon for Injection, this difference is unlikely to be of clinical significance.

Table 10: Incidence of Adverse Events by SOC

	Test Product A (N=31)		Reference Product B (N=29)		Overall (N=32)	
	n	(%)	n	(%)	n	(%)
Subjects With One or More Adverse Experiences	29	(93.5%)	26	(89.7%)	31	(96.9%)
Subjects With No Adverse Experience	2	(6.5%)	3	(10%)	1	(3.1%)
Gastrointestinal disorders	15	(48.4%)	11	(37.9%)	17	(53.1%)
Diarrhoea	2	(6.5%)	3	(10%)	5	(16%)
Nausea	10	(32.3%)	8	(27.6%)	14	(43.8%)
Vomiting	11	(35.5%)	7	(24.1%)	13	(40.6%)
General disorders and administration site conditions	24	(77.4%)	24	(82.8%)	29	(90.6%)
Asthenia	7	(22.6%)	4	(13.8%)	10	(31.3%)
Fatigue	1	(3.2%)	0	(0.0%)	1	(3.1%)
Injection site erythema	17	(54.8%)	19	(65.5%)	23	(71.9%)
Injection site swelling	18	(58.1%)	16	(55.2%)	24	(75.0%)
Vessel puncture site haematoma	1	(3.2%)	0	(0.0%)	1	(3.1%)
Vessel puncture site pain	1	(3.2%)	0	(0.0%)	1	(3.1%)
Investigations	10	(32.3%)	8	(27.6%)	15	(46.9%)
Blood glucose decreased	0	(0.0%)	1	(3.4%)	1	(3.1%)
Blood potassium increased	1	(3.2%)	0	(0.0%)	1	(3.1%)
Blood pressure decreased	7	(22.6%)	8	(27.6%)	12	(37.5%)
Blood pressure increased	1	(3.2%)	0	(0.0%)	1	(3.1%)
Haematology test abnormal	1	(3.2%)	0	(0.0%)	1	(3.1%)
Nervous system disorders	9	(29.0%)	6	(20.7%)	13	(40.6%)
Dizziness	3	(9.7%)	2	(6.9%)	5	(16%)
Headache	4	(12.9%)	1	(3.4%)	5	(15.6%)
Somnolence	2	(6.5%)	2	(6.9%)	4	(13%)
Syncope	0	(0.0%)	3	(10%)	3	(9.4%)
Skin and subcutaneous tissue disorders	1	(3.2%)	1	(3.4%)	2	(6.3%)
Hyperhidrosis	1	(3.2%)	1	(3.4%)	2	(6.3%)
Vascular disorders	3	(9.7%)	5	(17.2%)	7	(21.9%)
Pallor	3	(9.7%)	5	(17.2%)	7	(21.9%)
* Adverse events are classified according to MedDRA® Version 16.0.						
Test Product A: 1 mg (1 IU/mL) Glucagon for Injection (Fresenius Kabi USA)						
Reference Product B: 1 mg (1 IU/mL) of GlucaGen for Injection (Bedford Laboratories) Source: Table 14.3.1.1						

Source: From Table 14.1,1 CSR.

7.4.2 Laboratory Findings

Most of the study subjects had normal blood glucose levels at screening (65-99 mg/dL). Four subjects had abnormal blood glucose levels at screening: two subjects had low blood glucose and two subjects had high blood glucose levels at screening. None of these abnormal glucose values were reported to be clinically significant (i.e., no symptoms of hypoglycemia or hyperglycemia were reported), and these values did not preclude subjects' participation in the study.

On average, absolute neutrophils doubled from baseline to post-dosing with no meaningful differences between Glucagon for Injection and Listed Drug. Of note, these increases were not associated with clinically significant events. Although the reference range was exceeded at several time points after treatment, the increases reported were limited and did not appear to be clinically relevant. Mean white blood cells increased by approximately 2 and 4 units between baseline and post-dosing. There were no meaningful differences in the increases observed between Glucagon for Injection and Listed Drug and the increases observed were not clinically significant. A mean decrease in lymphocyte counts and percentage was observed between baseline and post-dosing. These decreases of approximately 11 to 19 % were similar between Glucagon for Injection and Listed Drug and were not clinically significant. Finally, no changes from baseline were observed for serum transaminase concentrations.

Reviewer's note: Transient increases in neutrophils after glucagon administration have been previously reported in the literature[1]. The precise mechanism of action is unknown. The increases reported here are not worrisome because of their transient nature and lack of clinical significance, particularly given that this drug is not intended for chronic use.

Individual Clinically Significant Abnormalities

Below are summarized narratives for four subjects who experienced laboratory abnormalities that were deemed clinically significant by the Applicant.

A 43-year-old male (Subject Four) experienced elevated serum potassium approximately four hours following administration of Glucagon for Injection (Period Two) (6.5 mmol/L; reference range: 3.5 - 5.2 mmol/L). No symptoms of hyperkalemia were reported and this laboratory abnormality resolved spontaneously four days later. This subject was on no other medications. ECG at screening was normal.

A 47-year-old male (Subject Six) experienced decreased serum glucose (38 mg/dL; reference range 65 - 99 mg/dL) approximately four hours following administration of the Listed Drug. The subject at the same time experienced pallor, syncope that resolved with support therapy, dizziness, and decreased blood pressure that resolved spontaneously. The next serum glucose levels obtained four days later was within normal range.

A 40-year-old female (Subject 29) experienced low hemoglobin 8.5 g/dL (reference range 11.1 - 15.9 g/dL), approximately four hours following administration of Glucagon for Injection. Hematocrit, MCV, and MCH values were also low. The subject's hemoglobin, hematocrit, MCV, and MCH values were below reference range also at screening and before dosing. The subject had also experienced at the time of dosing with Glucagon for Injection an AE of vomiting that resolved spontaneously within four hours from dosing. These two events are unlikely to be related to each other.

1 **Invest Radiol 1988; 23: 847-852**

A 32-year-old male (Subject 10) experienced an AEs of elevated serum ALT and AST concentrations. This AE occurred on Day minus One prior to dosing and therefore it is very unlikely to be related to study medication.

Reviewer's note: The review of these narratives does not raise clinical concerns, as the subjects were mostly asymptomatic. These findings appear to have been self-limited and were not associated with any other clinical sequelae.

7.4.3 Vital Signs

Vital signs were measured 15 minutes before and approximately 15 minutes after each injection. Blood pressure values remained within reference range with minimal changes from pre-dose and no reported differences between the study treatments. A similar number of subjects experienced the MedDRA preferred term of "decreased blood pressure" for a total of 16 times after Glucagon for Injection vs. GlucaGen (7 vs. 8 subjects). Most of the episodes took place 1.5 hours to 2.5 hours after dosing and resolved within five to 30 minutes without any treatment.

The age of the subjects who experienced decreased blood pressure ranged from 33 to 59 years old; 10 subjects were females. With the exclusion of Subject Six, a 47 year old male who, after taking GlucaGen had a blood pressure of 65/43 mmHg which was accompanied by an episode of syncope that resolved within 20 minutes, the diastolic blood pressure values in the other events did not decline below 60 mmHg.

Reviewer' note: The AEs of decreased blood pressure were expected, given the mechanisms of action of glucagon and the long-standing experience with glucagon administration. This adverse reaction is already included in labeling. No notable differences between the two study drugs were evident.

7.4.4 Electrocardiograms (ECGs)

A 12-lead ECG was performed only as part of the screening procedures. All enrolled subjects had normal ECGs at baseline.

7.4.5 Special Safety Studies/Clinical Trials

There were no *a priori* specific safety concerns that warranted special safety studies or clinical trials.

7.4.6 Immunogenicity

Immunogenicity studies were not conducted. Synthetic glucagon, administered as a single dose to aid in radiological examination, is not expected to pose immunogenicity risk. As indicated in a memo dated December 16, 2014 from Dr. Steven Bowen, Office of Biotechnology Products, Division of Therapeutic Products, immunogenicity assessments were not requested by the Agency because the sought after indication – (b) (4) as a diagnostic aid – is generally intended for one time use and immunogenicity was not thought to be of significant concern (see below).

Due to the weak immunogenicity of purified glucagon demonstrated in the studies outlined above, a post-marketing requirement for the sponsor to monitor immunogenicity of the glucagon drug product is not necessary.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time-Dependency for Adverse Events

The study design (i.e., four single-dose treatment periods) did not allow for a thorough evaluation of time-dependency of AEs. Specifically, there were no interim follow-up visits between the treatment periods; the interval between periods albeit always more than seven days was variable, and there was no follow-up assessment after the final study period (i.e., Period Four).

7.5.3 Drug-Demographic Interactions

Due to the relatively small sample size, the Applicant did not evaluate AEs by gender, age, or race. However, this reviewer noted that female subjects had approximately twice as many AEs than their male counterparts, an observation of unclear clinical significance.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant women were not included in the study. Glucagon does not cross the placenta.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no drug abuse potential with glucagon. As reported in product labeling for glucagon, overdosage may result in nausea, vomiting, gastric hypotonicity, as well as increases blood pressure and pulse rate. Since glucagon will be given as a single dose for radiological examination, there will be no risk for withdrawal or rebound.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Since Glucagon for Injection has not been approved for marketing in the US, there is no post-marketing experience at this time.

9 Appendices

9.1 Literature Review/References

Relevant references are cited within relevant sections of this clinical review.

9.2 Labeling Recommendations

Labeling recommendations are deferred to the CDTL memo.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GIOVANNI CIZZA
05/01/2015

LISA B YANOFF
05/01/2015

Please refer to my CDTL memo for a summary of the review findings for this application and to the Clinical Pharmacology review which contains the primary review for the pivotal relative bioavailability study for this NDA

Cross-Discipline Team Leader Review

Date	September 14, 2012
From	Karim Anton Calis, Pharm.D., M.P.H. Acting Clinical Team Leader Division of Metabolism and Endocrinology Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	201,849
Applicant	APP Pharmaceuticals A division of Fresenius Kabi USA, LLC
Date of Submission	November 30, 2011
PDUFA Goal Date	September 28, 2012
Proprietary Name / Established (USAN) names	Glucagon for Injection (synthetic)
Dosage forms / Strength	Sterile lyophilized powder for injection (1 mg per vial)
Proposed Indication(s)	As a diagnostic aid for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract
Recommendation:	*Complete Response*

Cross-Discipline Team Leader Review

1. Introduction

Glucagon is an endogenous hormone synthesized and secreted from the pancreatic alpha cells. Structurally, it is a 29-amino acid peptide, which acts on the liver to increase glucose production via glycogenolysis and gluconeogenesis, thereby effectively countering the effects of insulin. Two glucagon products—both produced from recombinant DNA expression—are currently approved in the United States for the treatment of severe hypoglycemia and also as a diagnostic aid to temporarily inhibit gastrointestinal motility. Novo Nordisk's GlucaGen was approved in 1998 under NDA 20,918. Shortly thereafter, Eli Lilly's Glucagon for Injection (no proprietary name) was approved under NDA 20,928.

This review addresses a new drug application for a synthetic glucagon for injection submitted by APP Pharmaceuticals (heretofore referred to as APP) under the 505(b)(2) pathway seeking approval only as a diagnostic aid for use (via intramuscular or intravenous injection) during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract. The applicant did not seek advice from the FDA prior to submission of this NDA.

APP's NDA relies on the Agency's findings of safety and effectiveness for the reference listed drug (RLD) GlucaGen, a product produced through recombinant DNA technology. APP mistakenly cites Bedford Laboratories' GlucaGen as the RLD. However, Bedford Laboratories does not manufacture a glucagon product but is a Novo Nordisk-authorized distributor of GlucaGen. In this review, references to Bedford Laboratories are made only insofar as to identify the specific source of the glucagon for injection product used by APP in their pivotal bioequivalence study. It should be noted that the amino acid sequences of the APP synthetic glucagon and the two U.S. approved recombinant glucagon products are identical to that of native human glucagon.

The current NDA submission, dated November 30, 2011, consists of chemistry data, nonclinical data (a bridging 4-week rat toxicology and toxicokinetics study along with findings from the AMES test and chromosomal aberration test), and a pivotal bioequivalence study. This NDA was granted formal clearance for action from the 505(b)(2) Coordinating Committee on August 27, 2012.

2. Background

NDA 201,849 was originally submitted by APP on September 30, 2010, but was subject to a refusal-to-file action because it was not sufficiently complete to permit a substantive review. APP's original application (b) (4) for use as a radiological diagnostic aid to temporarily inhibit the movement of the gastrointestinal tract. (b) (4)

(b) (4)

In their resubmission of NDA 201,849, the applicant addressed the refuse-to-file deficiencies (b) (4) Therefore, this memorandum reviews the resubmitted NDA as (b) (4) the diagnostic use indication and only to the intramuscular and intravenous routes of administration.

Of note, in our filing letter dated February 10, 2012, we advised the applicant that, while it is acceptable (b) (4) the diagnostic use indication (b) (4) we nonetheless encourage them to adequately differentiate their product from the other marketed glucagon products so that the APP product is used only as a diagnostic (b) (4)

3. CMC

Please refer to Dr. Olen M. Stephens' review for further details. The drug substance is a synthetic, single-chain 29-amino acid peptide (b) (4) The drug product is a sterile, white lyophilized powder for injection, packaged as 1 mg per vial. The inactive ingredients (lactose NF and Water for Injection USP) are the same as those used in GlucaGen, and all excipients are of Compendial quality. The product must be reconstituted with sterile water immediately prior to use.

As noted in Dr. Stephens' review, the applicant has agreed to tighten release and stability specifications for individual impurities, total glucagon-related impurities, total lactose-related impurities, assay by HPLC, and mass balance to reflect manufacturing capability as manufacturing experience is gained. Dr. Stephens noted that this re-evaluation of specifications should occur after the 10th commercial batch, but he concluded that it would not require a post-marketing commitment or a post-marketing requirement.

Dr. Stephens determined that the chemistry information is adequate, and that Chemistry, Manufacturing, and Controls (CMC) deficiencies for the drug substance and drug product have been adequately addressed by the applicant. Dr. Stephens concludes that there are no CMC

deficiencies that would serve as the basis for not allowing approval of the NDA. However, because the Office of Compliance has rendered a "withhold" recommendation (February 22, 2012), the CMC recommendation is nonetheless for a *Complete Response*. The withhold recommendation is based on unspecified deficiencies identified by an FDA field investigator during an inspection of the APP Pharmaceuticals facility located at 3159 Staley Rd, Grand Island, New York.

4. Nonclinical Pharmacology/Toxicology

Please refer to Dr. Indra Antonipillai's review for further details. The nonclinical data provided by the applicant consisted of a 4-week rat toxicology study and two in vitro gene toxicity studies (Ames and chromosomal aberration assay) comparing the APP drug product and the RLD GlucaGen.

Dr. Antonipillai notes that overall drug exposure in the 28-day rat toxicity study was similar for the two drug products tested. She also notes that the total impurities tested in the 28-day toxicity study were "up to (b)(4)% with the APP drug product and up to (b)(4)% with the listed drug GlucaGen." The safety of the drug product and impurities was adequately qualified in the 4-week bridging toxicity study in rats with only "subtle toxicity" noted with the APP product but not with the reference listed drug.

The target organs of toxicity may be the heart in female rats (minimal to mild mineralization in 2/8 rats at a the high dose of 5 mg/kg/day, but not noted with the reference listed drug or controls) and the kidney in male rats (minimal to mild bilateral chronic progressive nephropathy in 3/8 rats, but not noted with the reference listed drug or controls). Overall, Dr. Antonipillai concludes that the heart and kidney findings are mild and unlikely to have any clinical significance particularly if the product is used as intended (i.e., as a single-dose diagnostic).

Dr. Indra Antonipillai has determined that no deficiencies were found in this application, and no additional nonclinical studies are needed. On the basis of the nonclinical data provided by the applicant, Dr. Antonipillai, with concurrence from Dr. Karen Davis Bruno, concludes that this NDA can be approved from a pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Dr. Immo Zadezensky's clinical pharmacology review for further details. Study 200090101 is the only clinical study included this application. The primary objective of this study was to demonstrate the pharmacokinetic and pharmacodynamic bioequivalence of the APP Glucagon for Injection and the Novo Nordisk GlucaGen product following intramuscular injection. This was a single-center, randomized, single-dose, single-blind, two-treatment, four-period, replicate-design, crossover study conducted under fasting conditions in 32 healthy volunteers (25 actually completed the study). A 1-mg dose of both the test and reference

products was administered into the upper deltoid muscle, and a conservative 7-day washout period was used between doses to minimize the possibility of a carry-over effect.

Inclusion criteria included healthy male and female subjects at least 18 years of age who agreed to use adequate contraception during the study and for at least 28 days prior to the study. Exclusion criteria included the presence of various medical conditions, use of medications within 14 days of the study, clinically significant laboratory findings, and a positive pregnancy test.

A single, 1-mg intramuscular dose was to be administered to subjects following an overnight fast of at least 10 hours in each study period. The study participants received the APP product in two study periods and the reference product GlucaGen in the other two study periods (in a different arm during each period). The order of treatment administration was randomly assigned, and there was a 7-day interval between all treatment phases.

Venous blood samples were collected for pharmacokinetic and pharmacodynamic assessments at -2, -1, and -0.5 hours, and at 10, 20, 25, 30, 40, 50 minutes and at 1, 1.5, 2, 2.5, 3, and 4 hours following the 1-mg dose. Subjects were confined at the clinical facility from at least 12 hours prior to dosing until after the 4-hour blood collection.

The primary pharmacokinetic (glucagon) endpoints, as specified in the protocol, were $C_{max,}$ T_{max}, and AUC following a 1-mg dose of the study products. The primary pharmacodynamic (glucose) endpoints were peak glucose concentrations (C_{max}), defined as the maximum observed value, as well as T_{max}, and AUC.

The applicant used standard criteria to assess bioequivalence. Specifically, for each parameter of interest, the applicant declared bioequivalence if the calculated 90% confidence interval (CI) for the ratio of geometric means of APP to GlucaGen was contained within 80% to 125%.

Pharmacokinetic and Pharmacodynamic Results

Please refer to Dr. Zadezensky's complete review for the study results. Of note, all 25 study participants who completed the bioequivalence study were noted to be "Hispanic/Latino," and 13 were men. The median age was 39 (range 18-58), and the median body mass index was 27 Kg/m^2 (range 21-29). Results from study 20090101 demonstrate that the geometric mean ratio for both rate (C_{max}) and extent (AUC) of exposure for non-baseline corrected glucagon concentrations and the 90 % confidence interval fall within the 80-125% limit. The applicant also reported that the geometric mean ratio for both rate (C_{max}) and extent (AUC) of exposure for non-baseline-corrected and baseline-corrected glucose concentrations, and the 90 % confidence interval, fall within the 80-125% limit.

The complete pharmacokinetic and pharmacodynamic data are not presented in this memorandum because there were major deficiencies noted during the review process that could affect the interpretation of the study findings. Namely, the Office of Compliance rendered a "withhold" recommendation for deficiencies identified at an APP facility, and the Office of Clinical Pharmacology, in collaboration with the Office of Scientific Investigations, identified significant deficiencies in the bioanalytical assay for glucose measures (the primary

pharmacodynamic endpoint) which make the bioequivalence study not acceptable in support of approval.

According to Dr. Zadezensky, the applicant used a conventional diagnostic test procedure with single-concentration calibration for the glucose measurements. This method is not compliant with 21CFR320.29(a) and not consistent with the methodology recommended by FDA's Bioanalytical Method Validation Guidance. Of note, an information request during the course of the review revealed that the applicant did not retain plasma samples from their bioequivalence study. Therefore, a glucose re-assay of the samples using a validated method to potentially address this bioanalytical deficiency was not possible. Please refer to Section 11 of this memorandum for further details.

Upon re-examination of the case report forms, this reviewer also noted that the dosage and administration section refers only to intravenous administration of both study products, when in fact the bioequivalence study is a comparison of the two products following intramuscular injection. While this could simply have been a typographical error on the case report forms and not have affected the study conduct in any way, it nonetheless raises the possibility that the study investigators and/or their support staff could have erroneously administered the product by a different route (intravenous) rather than the intramuscular route specified by the applicant.

6. Clinical Microbiology

Please refer to Dr. John W. Metcalfe's review for details. Dr. Metcalfe notes that the product is aseptically dispensed into sterile containers and determined that no microbiology deficiencies were present in the application. On the basis of the data provided by the applicant, Dr. Metcalfe concludes that this NDA can be approved from a microbiology product quality perspective.

7. Clinical/Statistical- Efficacy

This application contains a single, clinical pharmacology (bioequivalence) study and no other clinical trials evaluating safety or efficacy of APP's synthetic glucagon product.
Please refer to Section 5 of this review for a discussion of the bioequivalence study design and the pharmacokinetic and pharmacodynamic findings.

Please refer to Section 8 of this review for a discussion of the safety findings from the single pivotal bioequivalence study.

8. Safety

As with effectiveness, the applicant is relying on the Agency's findings of safety for the listed drug GlucaGen. The bioequivalence study involved 32 healthy volunteers and was largely

unremarkable from a safety perspective. Adverse events were balanced between APP's glucagon and the reference drug GlucaGen (refer to Table 1), and there were no deaths or other serious adverse events involving these healthy study participants. However, 7 study participants withdrew from the study prematurely. As expected with glucagon, nausea was the most commonly reported adverse event, but injection-site reactions were not reported in the study.

A total of 24 adverse events (13 with the APP glucagon; 11 with GlucaGen) were reported by 12 of the 32 subjects who participated in bioequivalence study. Twenty-three of the adverse events were rated as mild and resolved spontaneously. The most frequently reported adverse events for the APP glucagon were nausea (5 participants) and vomiting (2 participants); the most frequently reported adverse events for the listed product GlucaGen were also nausea (4 participants) and vomiting (2 participants).

A total of 25 subjects completed the entire study and contributed to the bioequivalence findings.

The 7 subjects who discontinued the study prematurely were all noted to be "non-compliant with the study protocol." However, a closer examination of the case report forms revealed that 5 of the 7 participants also experienced one or more adverse events as follows:

-Subject 10 had nausea, diaphoresis, and looked "obtunded."

-Subject 12 had nausea and vomiting.

-Subject 13 had lightheadedness, nausea, vomiting, and blurred vision.

-Subject 19 had lightheadedness, nausea, vomiting, diaphoresis, and was also noted to be "obtunded."

-Subject 29 experienced vomiting.

Additional details regarding these study subjects were not available from the applicant.

Safety assessments included vital signs (at screening, within 15 minutes before dosing and 15 minutes and 4 hours after dosing), clinical chemistry (at screening and final discharge), hematology (at screening and final discharge), urinalysis (at screening and final discharge), pregnancy testing (at screening and Day -1), and 12-lead electrocardiogram (at screening and then only if clinically indicated).

Of note, the safety parameters obtained at the Screening visit could have been collected up to 14 days prior to the actual start of the study. Safety parameters such as clinical laboratory tests were only done at screening and at the end of the study. As such clinically significant findings could have been missed at the study outset, missed at various time points during the study, or falsely attributed to a particular study treatment. Also, routine examination of the injection sites was not specifically addressed in the study report.

The safety population consisted of all subjects who received at least one dose of study medication.

Adverse events were coded in tabular form using the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.1 for classification of adverse event data into system organ classes (SOC).

It should be noted that the applicant did not conduct immunogenicity assessments. DMEP has generally not required such studies for glucagon products because of the low potential for a simple peptide to induce an immune response and also based on the extensive clinical experience, albeit the body of experience is largely with the recombinant glucagon products.

Table 1. Treatment-Emergent Adverse Events (Safety Population)

System-Organ-Class Preferred Term	Study 20090101	
	APP Glucagon N=29 n (%)	**GlucaGen N=31 n (%)**
Gastrointestinal disorders		
Nausea	5 (17.2)	4 (12.9)
Vomiting	2 (6.9)	2 (6.4)
Nervous system disorders		
Dizziness	1 (3.4)	1 (3.2)
Headache	0	1 (3.2)
General disorders and administration-site conditions		
Weakness	1 (3.4)	0
Hyperhidrosis	1 (3.4)	0
Investigations		
Heart rate decreased	0	1 (3.2)
Triglycerides increased	0	1 (3.2)

Laboratory Data, Vital Signs, and Electrocardiograms:

Only one study participant, a 54-year-old man (Subject 23), was noted to have elevated triglycerides (1230 mg/dL) after receiving GlucaGen in the final phase of the study. The triglycerides were measured on the same day of the GlucaGen administration. The study participant apparently did not have any symptoms or complaints, and no explanations were provided by the applicant for this laboratory abnormality. Repeat labs five days later showed

the triglycerides had decreased to 752 mg/dL. A baseline triglyceride value was not provided, but the investigator had indicated on the case report form that all clinical laboratory tests were "normal." The study participant was subsequently lost to follow-up. The applicant attributed this event to GlucaGen, although this subject had also previously received the APP glucagon twice (21 days and 5 days prior to the aberrant laboratory finding).

None of the other subjects had clinically relevant changes in clinical chemistry, hematology, or urinalysis laboratories.

There were no clinically relevant changes in vital signs, and other than the screening at 12-Lead ECG at baseline, electrocardiograms were only to be done if clinically indicated.

9. Advisory Committee Meeting

Not applicable.

This NDA was not the subject of an advisory committee meeting mainly because glucagon is not a new molecular entity, and there is extensive clinical and regulatory experience with this simple peptide.

10. Pediatrics

This NDA application does not trigger the Pediatric Research Equity Act (PREA) because it does not provide for a new active ingredient, a new indication, a new dosage form, a new dosage regimen, or a new route of administration.

11. Other Relevant Regulatory Issues

Financial disclosures

Based on review of Form 3454, the applicant certified that neither of the two investigators reported potential financial conflicts of interest.

Office of Scientific Investigations

The Office of Scientific Investigations (OSI), Division of Bioequivalence and GLP Compliance (DBGLPC), conducted inspections of the clinical and analytical portions of Study 20090101. The analytical portion of glucagon measurement of the study was reviewed by DBGLPC scientist, Dr. (b) (4). Dr. (b) (4) concluded that the glucagon data from this study should be accepted for review. However, according to Dr. Immo Zadezensky, the Office of Clinical Pharmacology in collaboration with OSI identified significant deficiencies in the bioanalytical assay for glucose—the primary pharmacodynamic endpoint—thereby

rendering the glucose measurements unreliable. As a result of the deficiency related to the glucose measures, the clinical pharmacology team determined that the results of the pivotal bioequivalence study are not acceptable in support of approval. Please refer to Section 5 for additional details.

12. Labeling

The applicant based its proposed label on that of GlucaGen, which was recently approved in a Physician Labeling Rule (PLR) format. General labeling issues were discussed with the applicant, but a final label was not negotiated because the major deficiencies identified during the review process preclude approval of the application. Nonetheless, key labeling issues are summarized below insofar as they may apply to a future re-filing of this application. It should be noted that the proposed name for the APP product is Glucagon for Injection.

A potential risk from unintentional misuse of APP's glucagon for management of hypoglycemia stems from the fact that the product is not packaged with a syringe and diluent for rapid preparation and administration in an emergency situation. The proposed labeling for the APP product includes information pertaining only to the diagnostic use. The dosage and administration information for the diagnostic indication for use varies from that for the hypoglycemia indication. This may cause confusion and result in medication errors if the product were to be used inadvertently for the non-diagnostic use. Also, APP's product is labeled for IV and IM use, but not SC use. APP has not provided any evidence to confirm bioequivalence of the IM and SC routes for their glucagon product, and it is unknown if there are clinically important differences between the two routes in terms of onset of action.

APP has proposed a plan to mitigate potential risks form possible misuse of their product by differentiating their product from those approved for the hypoglycemia indication "through product design and marketing measures." APP specifically declined our recommendation to consider using a proprietary name for their glucagon product. However, APP proposed carton revisions to specify that their product is (b) (4) and their plan to mitigate risks also includes marketing measures such as education of their sales force and notification of major distributors and group purchasing organizations.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the container, carton, and package insert labels. Please refer to Dr. Jamie Wilkins Parker and Dr. Kellie Taylor's review for further details. DMEPA concludes that the warnings included on the proposed container labels and carton labeling adequately differentiate the APP product from glucagon products approved for the treatment of hypoglycemia. However, they recommend the following changes to the information displayed on the labels and labeling:

Container Label

1. Relocate the statement "For Diagnostic Use Only" to the principal display panel of the vial, and revise to state "For Diagnostic Use Only, Not Approved to Treat Hypoglycemia."

2. Revise the strength statement to state "1 mg per vial", and relocate the net quantity statement to a different location on the principal display panel, away from the strength statement, so that they are not confused.

3. We wonder if the statement "Glucagon as Hydrochloride 1 mg (b) (4)" is necessary. We suggest deleting the statement if it is not needed. If it is needed, we suggest relocating to the side panel of the label, and revise to state "Glucagon as Hydrochloride 1 mg" (b) (4)

4. Revise the NDC number of the vial to one which differs from that on the carton labeling.

Carton Labeling

1. Revise the strength statement to state "1 mg per vial", and relocate the net quantity statement to a different location on the principal display panel, away from the strength statement, so that they are not confused.

I agree with DMEPA's labeling recommendations, but I also propose adding an "Important Limitation of Use" section in the label to further clarify that the APP glucagon product is for diagnostic use only. The specific limitation of use should be included as follows: "This product is not intended for use to treat severe hypoglycemia because it is not packaged with a syringe and diluent necessary for rapid administration during an emergency."

13. Recommendations/Risk Benefit Assessment

I recommend a *Complete Response* primarily 1) because the Office of Compliance has rendered a "withhold" recommendation for deficiencies identified at the APP Pharmaceuticals facility in Grand Island, New York, and 2) because the results from the pivotal bioequivalence study are deemed unreliable based on the clinical pharmacology team's assessment of the analytical information provided by the applicant (i.e., deficiency in the analytical measurement of the primary pharmacodynamic endpoint). The only resolution to this deficiency is for the applicant to rectify the deficiencies that led to the Office of Compliance's *withhold* recommendation and to repeat the bioequivalence study and provide new data for FDA review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARIM A CALIS
09/24/2012

MARY H PARKS
09/24/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201,849	**Applicant: APP Pharmaceuticals**	**Stamp Date: 11/30/2011**
Drug Name: Glucagon for Injection	**NDA/BLA Type: 505(b)(2)**	**This is a resubmission after a refusal to file dated 12/8/2010.**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				This is a 505(b)(2) Application. The reference product is Novo Nordisk's GlucaGen. Note: The product in this application is synthetic—not recombinant like the reference product.
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Title: Sample Size: Arms: Location in submission:				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	The only pivotal trial is a bioequivalence study.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

N/A

Karim Anton Calis, Pharm.D., MPH 1/18/2012

Reviewing Medical Officer Date

Hylton V. Joffe, M.D., M.Sc. 1/18/2012

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARIM A CALIS
01/18/2012
Recommend Filing

HYLTON V JOFFE
01/18/2012

Proposed Meeting Preliminary Clinical Comments for NDA 201849

The following are proposed preliminary responses to the clinical questions posed by the applicant in an Information Package (serial 0004, SD 5, 1/28/11) pursuant to their December 30, 2011 correspondence requesting an informal meeting to discuss the refuse-to-file decision. There were no clinical refuse-to-file comments. The meeting with the applicant is currently scheduled for March 3, 2011.

FDA Comment D: Data sets for the bioequivalence (BE) study were not provided. Submit datasets that include patient identifiers and all measured safety parameters.

Sponsor Response: Adverse events (AEs) were collected and a tabular summary was provided for the BE study No 20090101. Unfortunately, the statistical analyses of these safety data (datasets) were inadvertently omitted from the submission. However, these datasets are available and do include identifiers and all measured safety parameters. These datasets will be provided in the resubmission.

A total of 24 adverse events (13, Test Product; 11, Reference Product) were reported by 12 of the 32 subjects who participated in this BE study. Twenty-three of the adverse events were considered "mild", of these, 22 resolved spontaneously prior to study completion and one resolved with treatment. One adverse event was considered "moderate" and had not resolved by the end of the study. The most frequent adverse events reported for the test product were nausea (5 subjects) and vomiting (2 subjects). The most frequent adverse events reported for the reference product were nausea (4 subjects) and vomiting (2 subjects).

A data listing and summary of all adverse events that includes patient identifiers can be found in Section 11.4 Appendix D of this response and these data were located in section 5.3.1.2 of the original NDA submission. A tabular summary of the frequency of AEs by body system is also provided in Section 11.4 Appendix D of this response.

Sponsor Question: Does the FDA concur that provision of the (SAS) data sets including the measured safety parameters for this study and that the submitted adverse events subject listings and tabular summary of AEs by body system will be adequate to characterize the safety data that is currently available?

Proposed FDA Preliminary Response: We understand that you plan to include the requested bioequivalence (BE) study data sets with your resubmission. We also understand that you plan to include participant identifiers and all measured safety parameters. For the clinical safety data, our preference is to receive them in SDTM and ADaM format (CDISC). Until we review these data we cannot comment on their overall adequacy. Also, we note that the BE study was conducted with 32 participants

but only 25 completed the study. A detailed explanation for the 7 dropouts should be provided in the NDA.

FDA Comment E: You are proposing the use of your product [redacted] (b) (4) for use as a diagnostic aid. The proposed commercial product as described in your application is to be supplied as [redacted] (b) (4)

[redacted] (b) (4)

FDA Comment G: You are proposing intramuscular, [redacted] (b) (4) and intravenous routes of administration for your product. However, your pivotal BE study only obtained data for the intramuscular route of administration [redacted] (b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARIM A CALIS
02/22/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201,849 **Applicant: APP Pharmaceuticals** **Stamp Date: 11/29/10**

Drug Name: Glucagon for Injection **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				This is a 505(b)(2) Application. The reference product is Novo Nordisk's GlucaGen. Note: The product in this application is synthetic—not recombinant like the reference product.
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Title: Sample Size: Arms: Location in submission:				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	The only pivotal trial is a bioequivalence study.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		
34.	Are all datasets to support the critical safety analyses available and complete?		X		
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____No___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

1. The refuse-to-file recommendation applies (b) (4) [redacted]

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Data sets for the bioequivalence (BE) study were not provided. Submit datasets that include all measured safety parameters.
2. Bioequivalence data provided are based on intramuscular administration only. (b) (4) [redacted]

Karim Calis, Pharm.D., MPH 11/29/10

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARIM A CALIS
11/30/2010
Clinical Filing Checklist

HYLTON V JOFFE
11/30/2010