CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-136 **Code: 3S**
Name: ———Synthetic Porcine Secretin) 16 mcg/mL vial
Sponsor: ChiRhoClin, Inc., Silver Spring, MD
Submission Type: Original NDA
Submission Dates: 5/14/99, 10/6/99, 12/29/99
Reviewer: Suresh Doddapaneni, Ph.D.

Synopsis

NDA 21-136 and NDA 21-209 deal with the same drug product, Synthetic Porcine Secretin, split up into two NDA's for administrative reasons. Therefore, the same Human Pharmacokinetics and Bioavailability (HPB) data was submitted in support of the two NDA's. NDA 21-136 seeks the approval of indications for (1) diagnosis of pancreatic exocrine —— and ———— NDA 21-209 seeks the indication of diagnosis of gastrinoma (——— A comprehensive Clinical Pharmacology and Biopharmaceutics (CPB) review was completed for NDA 21-209 by Dr. Ronald Kavanagh on February 10, 2000. In that review, a defferral of the submission of pharmacokinetic data for this product was granted in accordance with 21CFR 320.22(e). Since NDA 21-136 contains the same HPB data, the completed CPB review for NDA 21-209 is applicable to NDA 21-136 as well. Thus, the conclusions drawn and the review comments made in NDA 21-209 are applicable to NDA 21-136 also. Hence, the reader is referred to the CPB review of NDA 21-209 for all issues regarding NDA 21-136.

Recommendation

The Human Pharmacokinetics and Biopharmaceutics section of NDA 21-136 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. Comments A and B appearing on page 25 of the Clinical Pharmacology and Biopharmaceutics review of NDA 21-209 should be sent to the sponsor. In addition, the sponsor is also recommended to incorporate the information into the clinical pharmacology section of the package insert when data from the pending pharmacokinetic study is available.

[/S/] 3/9/00
Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist,
Division of Pharmaceutical Evaluation II

FT initialed by Shiew-Mei Huang, Ph.D.: [/S/] 3/9/00
Acting Division Director, DPEII
CC:
NDA 21-136 (Original), HFD-180 (Division Files, Strongin, Goldkind, Gallo-Torres, Aurecchia, Talarico), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Shiew-Mei Huang), CDR (Zom Zadeng).

Memorandum

Office of Clinical Pharmacology and Biopharmaceutics

NDA: 21-136

Title: Synthetic Porcine Secretin

Reviewer: Alfredo R. Sancho, Ph.D. Ref.: Filling Memorandum
Submission Date: 14 May 1999

Dosage: 16 µg strength Lyophilized Sterile Powder (Intravenous route).

Sponsor: ChiRhoClin, Inc.
Address: 15500 Gallaudet, Silver Spring, MD 20905

BACKGROUND

Secretin is a 27 amino acid peptide that is a naturally occurring gastrointestinal hormone in all mammalian species. Its physiological function is to stimulate the exocrine pancreas gland to secrete pancreatic juice with a high bicarbonate content and at the same time to flush out pancreatic digestive enzymes into the duodenum. This action alkalinizes the gastric contents entering the duodenum postprandially and provides the optimal chemical environment in terms of pH for proteolytic and lypolytic pancreatic enzymes to be biologically active.

Biologically derived porcine secretin, BPS, was approved by the FDA in 1981 as a diagnostic agent for evaluation of exocrine pancreas function and specifically for diagnosis of chronic pancreatitis, facilitation of collecting desquamated pancreatic duct cells to diagnose by cytopathology pancreatic cancer, and for diagnosis of gastrinoma in terms of stimulation of serum gastrin levels. It has been marketed in this country since 1981 by KABI and then since 1989 by Ferring.

In NDA 21-136 submission package, the sponsor has identified and proposed four distinct indications for this product:

1. Diagnosis of pancreatic exocrine —
3. Diagnosis of gastrinoma — , and,
4. Facilitation of — during ERCP.

In the Clinical Pharmacology section of this NDA submission, the sponsor provides only a pharmacodynamic study, CRC 97-1. There is a secondary pharmacodynamic study, CRC 98-1, included in the Clinical section of this NDA submission. In both of these pharmacodynamic studies, the approved Biological Porcine Secretin (BPS) and the sponsor proposed Synthetic Porcine Secretin (SPS) are compared. The approved Biological Porcine Secretin (extracted from pig intestine) is approximately — , the sponsor's Synthetic Porcine Secretin is said to be — The approved BPS product dosing is expressed in clinical units based on a validated cat bioassay rather than by weight based on chemical analysis as the impurities make chemical analysis difficult. The approved BPS product has theoretical potential of transmitting animal pathogens, as do all biologically sourced products.

The sponsor states that the proposed SPS product has been proven to have equivalent pharmacological activity and diagnostic efficacy to the approved BPS product. The sponsor also states that the proposed SPS product is well characterized by a validated, stability indicating HPLC assay and dosing is expressed in units of weight (micrograms). The sponsor includes in this NDA submission a compendium of literature published articles that characterize the Biological Porcine Secretin, NOT the proposed product.

The sponsor, ChiRhoClin, Inc. submitted this NDA package for review on May 6, 1999. Prior to this submission, there was a pre-NDA meeting with the sponsor on November 18, 1998. During the meeting, the sponsor presented the following question under "Human Pharmacokinetics and Bioavailability Section":

> *"Human pharmacokinetics for porcine secretin (biologically derived and synthetic) are provided by published papers submitted to the IND. ChiRhoClin believes these published data fully satisfy the pharmacokinetic requirements for NDA approval of synthetic porcine secretin. Since the final product is a solution, which is administered via intravenous bolus and infusion, no bioequivalence problem is expected for this formulation. Therefore, characterization of the pharmacokinetic profile after intravenous administration should be sufficiently documented by the published papers. Does the FDA agree with this conclusion?"*

In the approved minutes of the meeting, the Agency's response to the sponsor's question was:

> *"No. The submitted literature are not pharmacokinetic studies. Studies CRC 97-1 and 98-1 will be reviewed as pharmacodynamic studies. It is necessary to demonstrate that your drug product has the same pharmacokinetic profile as the approved drug product. Please refer to 21 CFR 320.24(b)(1)(I) for additional requirements or provide justification for a waiver per section 320.22."*

COMMENTS

The following comments should be forwarded to the sponsor:

1. The sponsor has not responded to the Agency's comment quoted immediately below (part of the minutes from the November 18, 1998 pre-NDA meeting) with either a pharmacokinetic study (with its resulting data) or a request for a waiver. The sponsor should appropriately respond to the following comment.

   > *"No. The submitted literature are not pharmacokinetic studies. Studies CRC 97-1 and 98-1 will be reviewed as pharmacodynamic studies. It is necessary to demonstrate that your drug product has the same pharmacokinetic profile as the approved drug product. Please refer to 21 CFR 320.24(b)(1)(I) for additional requirements or provide justification for a waiver per section 320.22."*

2. The approved Biological Porcine Secretin (BPS) is approximately — — while the sponsor's Synthetic Porcine Secretin (SPS) is said to be — This documented difference between the approved and the proposed product is another reason to require a pharmacokinetic study of the proposed product, for the behavior of the sponsor's product is NOT documented in any of the literature. The sponsor should provide their

rationale to why should the BPS literature articles be used to characterize the proposed SPS product when such differences exist between both products.

3. The sponsor proposed product in this NDA submission needs to be fully characterized, that is, this product's distribution, metabolism, elimination, protein binding, and special populations. There are no pharmacokinetic protocols, studies, nor data with the sponsor's product Synthetic Porcine Secretin in humans, healthy or otherwise. As part of this NDA submission, the structural information of this product and its comparison to the Biological Porcine Secretin should be included. The sponsor has included in this NDA submission a compendium of literature articles for the Biological Porcine Secretin, with the intent to use this literature information to satisfy the pharmacokinetic requirements for the proposed product, Synthetic Porcine Secretin. The sponsor should specifically outline which published literature articles refer to either product, BPS and SPS and which articles provide information in the following areas:

   - Structural and stability information of SPS, including possible "impurities",
   - Pharmacokinetic parameters of SPS, i.e., clearance,
   - Distribution of SPS, including volume of distribution,
   - Metabolism of SPS, including protein binding, and,
   - Behavior of SPS in Special population groups, including pediatrics.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacologic Evaluation II has reviewed the information and data submitted with this NDA on May 14, 1999. Based upon a preliminary evaluation of the provided information and literature, it is concluded that this NDA can be filed. The statements in the Comments section of this review should be sent to the sponsor in the "Acknowledgement Letter" and the "Information Request Letter", accordingly.

/S/ 23 July 99

Alfredo R. Sancho, Ph.D.
Pharmacologist/Pharmacokinetic Reviewer
Radiopharmaceuticals and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

[/S/] 7/23/99

David Lee, Ph.D
Team Leader, Pharmacokineticist
Gastrointestinal and Blood Clotting Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-180 NDA 21-136 (1x); DIV.FILE (1x); STRONGIN (1X); SANCHO (1X); LEED (1X); GALLOTORRES (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

APPEARS THIS WAY
ON ORIGINAL

NDA 21-136
NDA 21-209

This section is Not Applicable

[/S/] 3.27.02

Alice Kacuba, Regulatory Health Project Manager, HFD-180

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-136			
Submission(s):	Type: BZ	Suppl.: N/A	Letter Date: 5/8/00	Date Received: 5/9/00
Reviewer:	Sandip K. Roy, Ph.D.			
Team Leader:	Suresh Doddapaneni, Ph.D.			
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180			
Drug:				
Generic Name:	Synthetic Porcine Secretin			
Other Name(s):	sPS			
Trade Name:	[redacted]			
Molecular Weight:	3055.5			
Molecular Formula:	$C_{130}H_{220}N_{44}O_{41}$			
Structural Formula:	His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2			
Relevant IND(s)/NDA(s):	NDA 21-209			
Drug Class:	Peptide			
Dosage Form:	Lyophilized Sterile Powder for Injection			
Route of Administration:	Intravenous			
Dosing Regimen:	0.2 µg/kg body weight by IV injection over 1 min 0.4 µg/kg body weight by IV injection over 1 min (diagnosis of gastrinoma)			
Sponsor:	ChiRhoClin, Inc., Silver Spring, MD			
Proposed Indication:	• Diagnosis of gastrinoma (•			

SYNOPSIS

What is the purpose of this submission?

Data from a pending pharmacokinetic study has been submitted for this NDA. A deferral of the submission of pharmacokinetic data was granted in accordance with 21CFR§320.22(e), when regulatory action was taken on the original NDA submission.

Is the analytical method adequately validated?

A radioimmunoassay method was used which employs rabbit antisera, XAD-2 resin for rapid extraction of secretin from plasma, ^{125}I labeled secretin, [redacted]. This method is specific for porcine secretin and has been documented in reviews by Chang, T.M and Chey, W.Y. (Dig. Dis Sci. 25: 529-552) and Tia, H.H. and Chey, W.Y. (Anal Biochem. 87: 376-385, 1978). The standard curve in this RIA method included 11 secretin concentrations selected among 1, 2, 3, 5, 7, 10, 20, 30, 50, 70, 100, 200, and 300 pg. The resulting curve had a linear correlation coefficient (R) of 0.98 or greater. The precision and accuracy were not tested for this assay. Following data was provided based on repeated assay of human plasma sample containing endogenous secretin.

Limit of quantitation:	[redacted]
Intra-assay coefficient of variation:	<18%
Inter-assay coefficient of variation:	18%

What pharmacokinetic information about synthetic porcine secretin was provided under this submission?

Following pharmacokinetic parameters were obtained from a single dose study of 0.4 μg/kg sPS conducted in 12 normal subjects.

Clearance (ml/min)	487.2 ± 136.3
V_d (ml)	1938.2 ± 579.2
α-$T_{1/2}$ (min)	2.74 ± 0.32
β- $T_{1/2}$ (min)*	27.4

*Calculate by reviewer

After IV bolus administration, the plasma porcine secretin concentration rapidly declines to baseline secretin levels within 60 to 90 minutes in most of subjects. The mean AUC observed, which represented sampling to 120 min was nearly 78% of the estimated $AUC_{0-\infty}$. The α-half-life (distribution phase) of porcine secretin is 2.74 ± 0.32 minutes. The β-half-life (elimination phase) was calculated as 27.4 min. The clearance for porcine secretin is 487.2 ± 136.3 mL/minute and the volume of distribution is about 2 liter.

RECOMMENDATION

Comments:

- The sponsor has not resolved the physical stability issue [redacted], that was raised in the original review (Ronald Kavanagh, Ph.D.).

Labeling review:

Following labeling changes are recommended in the proposed package insert under "CLINICAL PHARMACOLOGY", "Pharmacokinetics" section.

Changes are indicated by strikethroughs (deletions) and underlined (additions) text:

[redacted]

APPEARS THIS WAY
ON ORIGINAL

[/S/]

Sandip K. Roy, Ph.D.
Clinical Pharmacologist

7/27/2000
Date

FT initiated by Suresh Doddapaneni, Ph.D. [/S/] 7/27/00

c.c. /NDA [redacted]
/HFD-180 (Division files, BStrongin)
/HFD-870 (SDoddapaneni, SHuang, SRoy)
/CDR (ZZadeng)

APPEARS THIS WAY
ON ORIGINAL

A. Pharmacokinetics **Report number CRC99-10**

Study Title **A Single Center Study Evaluating the Pharmacokinetic Profile of Single Intravenous Dose of Synthetic Porcine and Synthetic Human Secretin. Vol. 1.2, p 64. Protocol No. CRC99-10.**

Rationale: The purpose of this study is to characterize the pharmacokinetic profiles of single, IV dose of sPS and sHS products at a dose of 0.4 μg/kg in normal subjects.

Prinicipal Investigator Krishna Talluri, M.D.

Analytical Facility: [redacted]

Study Initiation date: November 10, 1999

Objectives

1. To determine the pharmacokinetic profiles of one dose of ChiRhoClin's sPS and one dose of sHS administered intravenously at 0.4 μg/kg
2. To evaluate the effect of sPS and sHS on serum gastrin levels in normal subjects
3. To evaluate the safety and tolerance of sPS and sHS in normal subjects

Study Design A sequential, uncontrolled, single dose study of the pharmacokinetic profiles of 0.4 μg/kg sPS and sHS given one week apart in 12 normal subjects

Subjects Age: 21 – 39 yrs (mean = 29.5 yrs)
Weight: 61.4 – 100.5 kg (mean = 77.2 kg)

Treatments Single intravenous bolus doses of sPS (0.4 μg/kg) and sHS (0.4 μg/kg) over 60 seconds were administered one week apart

Methodology

Blood samples: Collected at 0, 2, 4, 6, 8, 10, 15, 20, 30, and 45 min and 1, 1.25, 1.5, and 2 hrs after dosing with sPS and sHS.

Analytical Methods: A radioimmunoassay method was used which employs rabbit antisera, XAD-2 resin for rapid extraction of secretin from plasma, ^{125}I labeled secretin, and [redacted] The precision and accuracy were not tested for this assay. Following data was provided based on repeated assay of human plasma sample containing endogenous secretin.

Limit of quantitation:	[redacted]
Intra-assay coefficient of variation:	<18%
Inter-assay coefficient of variation:	18%

Pharmacokinetics: Pharmacokinetic parameters determined are AUC, C_{max}, $t_{1/2}$, Cl, K_{el}, and V_d.

Pharmacodynamics: Serum gastrin concentrations were assessed at baseline and at 2, 4, 10, 15 and 30 min post administration of sPS and sHS.

Results

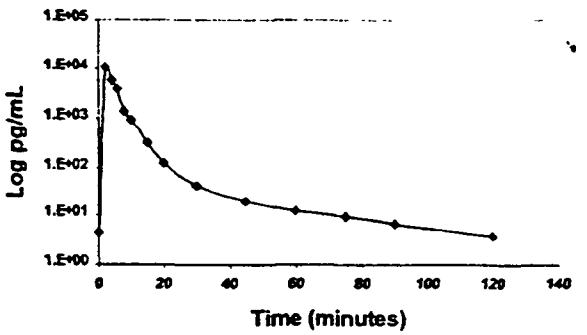
Clinical

There were no adverse effects reported for sHS. During the treatment period A (sPS), four subjects had 12 adverse effects. These adverse effects included headache, nausea, lightheadedness, numbness and tingling in the left hand, pallor, diaphoresis and hypotension. These adverse effects lasted 10 to 75 min and resolved without specific treatment.

Pharmacokinetics

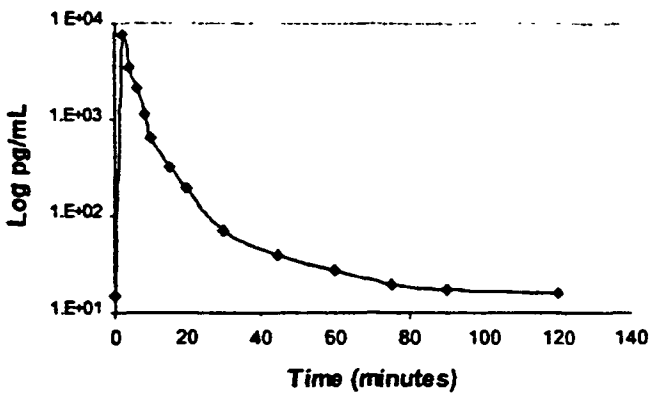
Synthetic Porcine Secretin:
After IV bolus administration, plasma concentration of porcine secretin concentration rapidly declined to baseline secretin levels within 60 to 90 minutes in most of the subjects. The mean AUC observed, which represented sampling to 120 min was nearly 78% of the estimated $AUC_{0-\infty}$. The α-half-life of porcine secretin is 2.74 ± 0.32 minutes. The β-half-life was calculated as 27.4 min. The clearance of synthetic porcine secretin is 487.2 ± 136.3 mL/minute and the volume of distribution is about 2 liter.

Mean Porcine Secretin Plasma Concentrations



Synthetic Human Secretin:
After IV bolus administration, plasma concentration of synthetic human secretin rapidly declined to baseline secretin levels within 60 to 90 minutes in most of subjects. The mean AUC observed, which represented sampling to 120 min was nearly 79% of the estimated $AUC_{0-\infty}$. The α-half-life of porcine secretin is 3.26 ± 0.28 minutes. The β-half-life was calculated as 45 min. The clearance synthetic human secretin is 580.9 ± 51.3 mL/minute and the volume of distribution is 2.7 liter.

Mean Human Secretin Plasma Concentrations



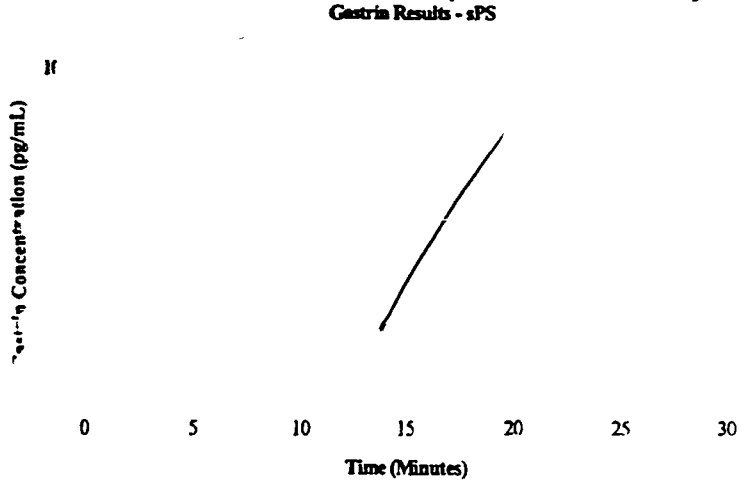
Summary of Pharmacokinetic Parameters for Synthetic Porcine and Human Secretin

Parameters	sPS	sHS
Clearance (ml/min)	487.2 ± 136.3	580.9 ± 51.3
V_d (ml)	1938.2 ± 579.2	2715 ± 2.3
α-$T_{1/2}$ (min)	2.74 ± 0.32	3.26 ± 0.28
β- $T_{1/2}$ (min)*	27.4	45.0

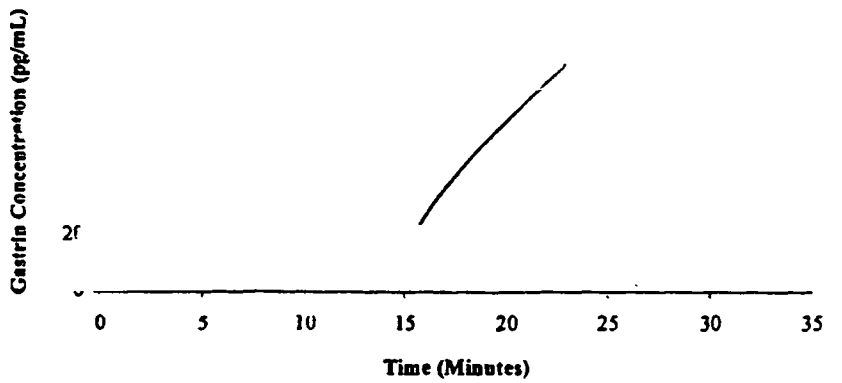
*Calculate by reviewer

Pharmacodynamics

sPS and sHS had minimal effects on serum gastrin concentrations in normal volunteers. The maximum increase from baseline in an individual was 24 pg/ml (34 to 58 pg/ml at 2 min) for sPS and 32 pg/ml (63 to 95 pg/ml at 4 min) for sHS. A threshold increase of 110 pg/ml is used as the diagnostic paradigm for gastrinoma. Gastrin levels returned to near baseline by 15 min in most subjects and by 30 min in all.



CRC99-10PK for Synthetic Human Secretin Gastrin Results



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FEB 10 2000

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-209 (References NDA 21-136)
Type of Submission:	1P
Generic Name:	Synthetic Porcine Secretin
Other Name(s):	sPS
Formulation; **Prescription Status;** **Strength** **Route of Administration**	Lyophilized Sterile Powder for Injection RX 16 mcg / 10 ml vial IV
Brand Name:	
Sponsor:	ChiRhoClin, Inc. Silver Spring, MD
Submission Date(s):	Letter Date / Date Received / Submitted Under / Comments 03 Feb 2000 / 03 Feb 2000 / NDA 21-209 / Interim Report 29 Dec 1999 / 30 Dec 1999 / NDA 21-136 / Interim Report 06 Oct 1999 / 07 Oct 1999 / NDA 21-136 14 May 1999 / 25 May 1999 / NDA 21-136
Reviewers:	Ronald Evan Kavanagh, B.S Pharm , Pharm.D., Ph.D.

I. BACKGROUND - NDA 21-209

A. Proposed Indication:

Diagnosis of Gastrinoma

B. Proposed Dose

0.4 µg/kg (2 µg/ml) over 1 minute for the indication of Diagnosis of Gastrinoma

0.2 µg/kg (2 µg/ml) over 1 minute for other indications (See Paragraph I.D.1 on Page 1)

C. Pharmacology

Secretin is a naturally occurring hormone that is released in response to ingestion of protein and other substances. It results in the release of pancreatic juice. Pancreatic juice contains various enzymes responsible for proteolysis, plus high concentrations of bicarbonate. The bicarbonate results in the alkalinization of the contents of the small intestines. Secretin also results in the release of gastrin and causes a decrease in the sphincter pressure of the pancreatic duct.

D. Background and History

1. History of NDA 21-209

NDA 21-136 for ' (synthetic porcine secretin; sPS) was submitted May 14, 1999 and received May 25, 1999. It sought approval for the following indications:

1) Diagnosis of pancreatic exocrine
2)
3) Diagnosis of gastrinoma
4) Facilitation of ; during ERCP

On July 22, 1999 a refuse to file letter was sent for indications #3 and #4. On October 13, 1999 the sponsor formally requested that these indications be filed "over protest". After being informed that filing indication # 4 would require payment of a user fee; on October 15, 1999 the sponsor requested that only indication #3 Diagnosis of gastrinoma, , be filed over protest.

Since, indication #3 Diagnosis of gastrinoma, , was a priority review category, whereas indications #1 and #2 were not, the indications were split into separate NDAs with separate NDA numbers. NDA 21-209 is for Diagnosis of Gastrinoma, ( ); and NDA 21-136 is for indications #1 and #2. Rather than recompile the data previously submitted under NDA 21-136, NDA 21-209 simply references material in NDA 21-136.

2. Biologically Sourced Porcine Secretin

Biologically sourced porcine secretin (bPS) was approved in 1981, however it was removed from the market by the manufacturer for commercial reasons synthetic porcine secretin (sPS), is a replacement product from a different source. bPS is approximately pure, whereas sPS should be nearly 100% pure. The activities of the peptide impurities in bPS are unknown.

II. SYNOPSIS

What regulatory issues are there?

This is a 505(b)(2) application since part of the evidence relies upon data obtained from the literature.

A waiver for the pharmacokinetic data for this product based on 21CFR§320.22(b)(1) is not appropriate for the following reasons:

a. It does not contain the same inactive ingredients as bPS
b. It has not been demonstrated that it contains the same active ingredient(s) as bPS
c. The NDA for bPS may have been withdrawn (although this reviewer is unable to confirm this at the present time)
d. bioavailability is not self-evident since there are physical stability issues (i.e. adsorption to glass and plastic) that may result in administration of doses different from the intended dose

In accordance with 21CFR§320.22(e), a deferral of the submission of pharmacokinetic data for NDA 21-209 may be granted.

Are there any stability issues?

Yes, secretin .. Consequently, this could effect the amount of hormone administered or assayed. Differences in the impurity profiles between bPS and sPS could result in different degrees of adsorption with the two products, and thus different dosages. No information was provided to address the stability issue.

Is the assay validation data acceptable?

No, there were no complete validation data provided for any pharmacokinetic study.

What pharmacokinetic data are available?

Data are primarily from literature citations using various sources of synthetic and biologic porcine secretin. These studies use various administration regimens. Because of differences in formulation factors (i.e. impurities) and in dosage regimens, these studies cannot be used to provide data for — . In addition, none of the presently available pharmacokinetic data utilize the same product or same administration regimen as the to be marketed product. The results are can thus only be used as supportive data.

In general, it appears that porcine secretin has a half-life of minutes and based upon data from the dog should be catabolized by a variety of tissues. Thus, there should not be problems in elimination various disease states such as chronic renal failure and possibly hepatic insufficiency. Data from pharmacokinetic studies with — in normal volunteers are pending, but were not be submitted in time for review.

III. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA # 21-209 and NDA #21-136. The Human Pharmacokinetic Section for NDA # 21-209 is approvable, provided there is an adequate resolution of the physical stability issue. In accordance with 21CFR§320.22(e), the pending data from the pharmacokinetic study that is currently in progress is deferred and should be submitted as a phase IV commitment for NDA #21-209. Please see paragraph VIII Labeling on page 25 and paragraph IX Comments for the Sponsor on page 25 and forward additional comments to the sponsor as appropriate.

APPEARS THIS WAY
ON ORIGINAL

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IV. REGULATORY ISSUES

A. Section 505(b)(2) Application

The sponsor is submitting this NDA under section 505(b)(2).

The sponsor claims in their letter of February 3, 2000 that guidelines to industry published in 1998 that 505(b) (2) applications can be approved based upon the demonstration of pharmacologic equivalence. In addition, that secretin is an example of a drug that would be eligible and appropriate for approval based on pharmacologic equivalence for the following reasons:

1) The sole active moiety is the same in bPS and sPS.
2) The formulations are not substantially different
3) The route of administration is intravenous, consequently, bioequivalence is assumed

Reviewer Comments:

This reviewer was unable to find the 1998 guideline the sponsor refers to.

According to the Draft Guidance for Industry: Applications Covered by Section 505(b)(2) July 20, 1999

'A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted". (21USC355(b)(2)).

That is it's a literature based NDA.'

The guidance does not mention secretin specifically but gives *Naturally derived or recombinant active ingredients* as a category that *might* fall under 505(b)(2).

A 505(b)(2) application still requires bioavailability/biocomparison data. The sponsor's arguments for not requiring bioavailability data may be based upon a proposal from OCPB that the sponsor may wish to request a waiver of the bioavailability requirement.

B. Requested Pharmacokinetic Studies vs. Waiver

At the November 18, 1998 Pre-NDA meeting and again in a letter from the FDA dated July 27, 1999 the sponsor was requested to submit the following.

> *'Either a complete study report from an appropriate pharmacokinetic study or a request for a waiver of the requirement.'*

Currently, neither a complete study report nor a request for a waiver has been submitted for review.

In their response (letter date October 6, 1999; page 000388) the sponsor failed to request a waiver. This is clearly indicated by a request for a meeting to discuss if a waiver *'is best considered'*.

In this reviewer's opinion, synthetic porcine secretin is not eligible for a waiver under 21CFR§320.22(b)(1)(ii). Since it does not meet the regulatory requirements for a parenteral solution intended solely for injection as delineated in 21CFR§320.22(b)(1)(ii):

'Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.'

In addition, the sponsor stated in their response:

'ChiRhoClin considers the pharmacokinetic data for IV bolus porcine secretin solution to be independent of formulation factors effecting the pharmacokinetics of porcine secretin for the diagnostic indications. As such, the extensive body of pharmacokinetic data in the literature should not be ignored in labeling of synthetic porcine secretin. Presently, the pharmacokinetic data currently available should provide adequate labeling...'

There are a number of potential differences between biologic and synthetic secretin, which could result in clinical differences. Consequently, the biologically sourced secretin is not necessarily an appropriate source of information for the synthetic secretin. For example, some of the impurities could have different activities and different kinetics from secretin resulting in differences in the measured pharmacokinetic-pharmacodynamic relationships. Alternatively, there could be differences in physical stability. For example, the impurities in bPS might increase the physical stability of secretin by minimizing the adsorption of secretin to glass and plastics. This might then result in differing dosages administered for the same *in vitro* activity of bPS and sPS.

A waiver may also not be granted based on the pharmacodynamic data since it is technically feasible to obtain pharmacokinetic information for this compound.

According to 21CFR§320.22(e), for a 'Full New Drug Application' the submission of *in vivo* bioavailability data may be deferred if it is compatible with the protection of the public health. Since, there are currently no longer any supplies of bPS available and as secretin is the only diagnostic medication for Zollinger-Ellison Syndrome, a deferral is appropriate.

Although waivers may be granted according to 21CFR§320.22(e), in this reviewer's opinion, a waiver should not be granted at the present time. Since the results of a pharmacokinetic study are pending

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V. CHEMISTRY

A. Drug Substance

1. Description

Porcine secretin is a 27 amino-acid polypeptide. Porcine and bovine secretin are identical to each other, but they differ from human secretin at amino acid positions 15 and 16.

Molecular Weight 3055.5

Empirical Formula: $C_{130}H_{220}N_{44}O_{41}$

Structural Formulae:

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Porcine	H-	His-	Ser-	Asp-	Gly-	Thr-	Phe-	Thr-	Ser-	Glu-	Leu-	Ser-	Arg-	Leu-	Arg-	**Asp-**	**Ser-**	Ala-	Arg-	Leu-	Gln-	Arg-	Leu-	Leu-	Gln-	Gly-	Leu-	Val-	NH_2
Bovine	H-	His-	Ser-	Asp-	Gly-	Thr-	Phe-	Thr-	Ser-	Glu-	Leu-	Ser-	Arg-	Leu-	Arg-	**Asp-**	**Ser-**	Ala-	Arg-	Leu-	Gln-	Arg-	Leu-	Leu-	Gln-	Gly-	Leu-	Val-	NH_2
Human	H-	His-	Ser-	Asp-	Gly-	Thr-	Phe-	Thr-	Ser-	Glu-	Leu-	Ser-	Arg-	Leu-	Arg-	**Glu-**	**Gly-**	Ala-	Arg-	Leu-	Gln-	Arg-	Leu-	Leu-	Gln-	Gly-	Leu-	Val-	NH_2

2. Manufacturing Site - Bulk Substance

[redacted]

B. Drug Product

1. Description

sPS is provided as a sterile lyophilized powder containing 16 mg of sPS, and 20 mg L-Cysteine HCl monohydrate, plus mannitol in a 10 cc — glass vial.

2. Formulation

a) sPS Batch Formulation

Table 1 sPS Batch Formulation[1]

Component	Amo
Synthetic Porcine Secretin	
L-Cysteine HCl monohydrate	
Mannitol	

1 Makes approximate — dosage units

b) sPS Finished Product Composition

Table 2 sPS Composition of Finished Product

Component	Amount / Vial
Synthetic Porcine Secretin	16 µg
L-Cysteine HCl monohydrate	
Mannitol	

(1) Reconstitution

According to the proposed labeling, the drug product is to be reconstituted with 8 ml of 0.9% Sodium Chloride for Injection USP to provide a 2 µg/ml solution with a final pH of 3.0 to 6.5.

3. Manufacturing Site - Finished Product

Drug product is manufactured at:

Chesapeake Biological Laboratories (CBL)
Baltimore, MD

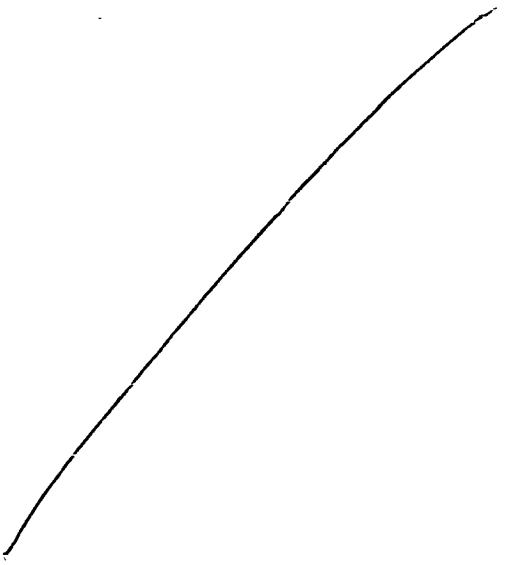
4. Stability

a) Lyophilized Product

Stability information was not provided. However, storage recommendations of -20 °C, indicate the possibility of a chemical stability issue.

b) Reconstituted Product

Stability information on the reconstituted product was not provided. If the product is not chemically and/or physically stable, variations in efficacy and safety could occur without adequate instructions.



Without detailed stability information, the potency of the product, the dosage, and the pharmacokinetics of secretin cannot be defined, nor can the pharmacokinetics or pharmacodynamics be unambiguously compared to bPS.

For labeling purposes, the sponsor will need to define the stability and/or conditions of use of secretin to account for and minimize any stability issues. Factors that need to be examined include

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ON ORIGINAL

VI. ANALYTICAL METHODS

A. Assay Validation

At least 4 different assays were used. There was no acceptable assay validation or in-process quality control data presented for any assay.

Table 3 Summary of Assay Validation Data Used in Published Pharmacokinetic Studies

Reference	Assay Type	Assay Validation	Comments
You et al. Gastroenterol 1983	Not mentioned	Not mentioned.	Only information provided regarding this study was a photocopy of a single figure and its' legend
Kolts and McGuigan Gastroenterol 1977	RIA	Included in article	Limited and inadequate information
Christ et al. Gastroenterol 1988	RIA	Data not included	Limited validation data included in article. Article cites 2 references for assay validation data, however these were not provided by the sponsor
Carr-Locke et al. Dig Dis Sci 1985	RIA	Review article cited and included	Reference Chang and Chey[1]

1. Chang and Chey Article

The Chang and Chey article has two main sections. The first section reviews the issues surrounding radioimmunoassays for secretin and the second reviews the kinetic literature across a wide variety of species and substances. There is only a limited section on assay validation discussing it in general terms.

The assay variability data presented in the article was based on repeated analysis of unspiked samples from fasting dogs. This suggests that endogenous dog secretin was being measured. This would not detect any bias in the assay.

Table 4 Chang and Chey Article - Published Assay Variability Data

	Measured Concentration - (pg/ml) Mean ± SD (CV)
Intraassay variability (n= 3)	9.3 ± 1.4 (15.0%)
Interassay variability (n= 10)	9.7 ± 1.9 (19.5%)

Since there are endogenous interfering substances, by the author's own admission actual variation would be much higher with samples from multiple subjects. For these and other reasons, the data presented above are non-informative.

In addition, there is no indication that this was the same reagent batch or procedure used for the 'clinical samples', nor is there any indication that it would apply to porcine secretin.

[1] Chang T and Chey WY; Radioimmunoassay of Secretin: A Critical Review and Current Status. Digestive Diseases and Sciences, 1980: 25 (7) 529-552.

2. Kolts and McGuigan Article

Insufficient data were presented. It was claimed that the sensitivity of the assay was 12.5 pg/ml. It was also claimed that it was specific. That is it's 1000 fold less sensitive for GIH Cholecystokinin-Pancreazyme (CCK-PZ) than for secretin.

B. Stability

C. In-Process Quality Controls and Raw Data

There was no mention of any in-process quality control procedures or raw data for any assay or study.

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ON ORIGINAL**

VII. PHARMACOKINETICS

1. Sources of Pharmacokinetic and Pharmacodynamic Data

Information from six literature sources and one study performed by the sponsor were included to provide data on the pharmacokinetics of secretin.

These included the following citations:

Kolts BE and McGuigan JE.
Radioimmunoassay Measurement of Secretin Half-life in Man.
Gastroenterology. 1977; 72(1) 55-60.

You CH, Rominger JM, and Chey WY.
Potentiation Effect of Cholecystokinin-octapeptide on pancreatic bicarbonate secretion stimulated by a physiologic dose of secretin in humans.
Gastroenterology. 1983; 85, 40-45.

Carr-Locke DL, Gregg JA, and Chey WY.
Effects of Exogenous Secretin on Pancreatic and Biliary Ductal and Sphincteric Pressures in Man Demonstrated by Endoscopic Manometry and Correlation with Plasma Secretin Levels.
Digestive Diseases and Sciences. October 1985; 30(10) 909-917.

Burhol PG, Jenssen TG, Florholmen J, and Jorde R.
Protein-binding of Secretin in Human Plasma.
Acta Physiologica Scandinavia. 1985; 123, 339-347.

Christ A, Werth B, Hildebrand P, Gyr K, Stalder GA, and Beglinger C.
Human Secretin: Biological Effects and Plasma Kinetics in Humans.
Gastroenterology. 1988; 94(2) 311-316.

Chey WY and Chang TM.
Secretin Chapter 17
Handbook of Physiology - The Gastrointestinal System II. (Year unavailable) 359-402.

Protocol CRC99-10
A Single Center Study Evaluating the Pharmacokinetic Profile of a Single Intravenous Dose of Synthetic Porcine and Synthetic Human Secretin in Normal Subjects. (Submitted February 3, 2000)

2. Routes of Elimination

No information on routes of elimination was provided for humans. However, in dogs it appears that catabolism occurs in the kidney. Catabolism also likely occurs in other highly perfused tissues as well. Consequently, it's unlikely that there would be problems with elimination with a drug such as this that is administered as a single dose and that has a half-life of minutes but a prolonged pharmacodynamic response (i.e. $\geq$ 1 hour).

3. Types and Sources of Secretin Used in Pharmacokinetic Studies

As shown in Table 5 none of the secretin used in five of the pharmacokinetic studies match the proposed to be marketed product. Since the type of secretin, purity, etc. from each of these sources cannot be compared to the proposed to be marketed product; any extrapolation to [redacted] is purely supportive.

Table 5 Types and Sources of Secretin Used in Pharmacokinetic Studies

Reference	Type of Secretin	Source
You et al. Gastroenterol 1983	Not mentioned	Not mentioned.
Kolts and McGuigan Gastroenterol 1977	Purified Porcine Secretin from Biologic Sources	Gastrointestinal Hormone Research Laboratory Karolinska Institute, Stockholm Sweden
Chrst et al. Gastroenterol 1988	Synthetic Porcine Secretin (Sekretolin)	Hoescht Pharma, Zurich Switzerland
	Synthetic Human Secretin	Peninsula Laboratories Belmont,Calif.
Carr-Locke et al. Dig Dis Sci 1985	Synthetic Secretin (Type not mentioned - could be human)	Squibb & Sons, Inc. Lot No. UTQ-000-H/U-6
Study 99-10	[redacted]	
Burhol et al. Acta Physiol Scand 1985 (Protein Binding Study)	Not mentioned.	Appears to be from Kabi Vitrum, Stockholm Sweden

4. Pharmacokinetic Studies

a) Studies with [redacted]

(1) Study 99-10

An interim study report was submitted in late December 1999 (letter date December 29, 1999) for study 99-10 and a study synopsis was submitted 03 February 7, 2000. This study examines both PK and the PD effect on gastrin secretion. No pharmacokinetic data was submitted with either submission. Consequently, the study was not reviewed.

b) Studies with Other Porcine Secretins

(1) Study 1

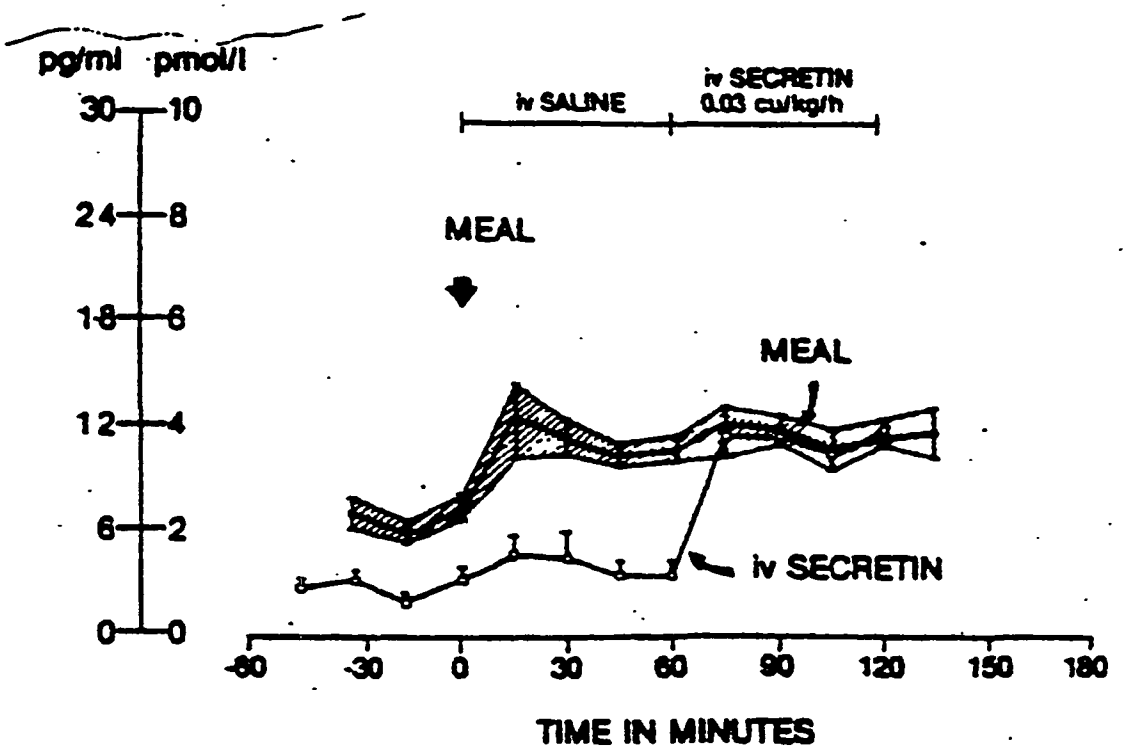
You CH, Rominger JM, and Chey WY.
Potentiation Effect of Cholecystokinin-octapeptide on pancreatic bicarbonate secretion stimulated by a physiologic dose of secretin in humans.
Gastroenterology. 1983; 85, 40-45.

A single figure from this study was provided, without any additional information.

The type of secretin used in this study is unknown.

Based upon the information provided, the figure does not make sense (See Figure 1). The baseline secretin concentrations in the 30 healthy subjects who received a meat meal are approximately double the baseline concentration in the 15 healthy subjects who received a secretin infusion. Secretin concentrations do not decrease after the meal or after the end of the secretin infusion. The dose of secretin also seems to indicate that the type of secretin used may not be the same as the proposed to be marketed product.

Figure 1 Secretin Concentrations after a Meat Meal or During a Secretin Infusion



The legend to this figure reads:

"Plasma secretin concentrations after a standard meat meal in 30 healthy subjects and during intravenous infusion of 0.03 CU • kg^{-1} • hr^{-1} (2.8 pmol • kg^{-1} • hr^{-1}) of GIH secretin, dissolved in 0.2% albumin, in 15 healthy subjects....*Shaded area*, means ± SE of plasma secretin concentration after a meal. Each *point* and *bar* represent mean ± SE."

Using the following rate of infusion and approximate mean steady state concentrations determined from the figure:

Rinf	2.8 pMol/hr • kg^{-1}	(0.03 CU/hr • kg^{-1})
Cp^{ss}	4.0 pMol/L	
Cp^{ss}_{corr}	3.0 pMol/L	Correcting for a baseline of 1.0 pMol/L and assuming no change in endogenous secretin release into the systemic circulation

The estimated average clearance for a 70 kg person ranges from 49 L/hour (817 ml/min) without baseline correction to 65.3 L/hour (1089 ml/min) with baseline correction.

Since a new steady-state is reached within 15 minutes of starting the secretin infusion, this indicates a half-life of a few minutes. Consequently, secretin concentrations should decline to baseline within 15 minutes of stopping the infusion, however, the figure shows no decrease in secretin concentrations 15 minutes following the end of the infusion.

(2) Study 2

Kolts BE and McGuigan JE.
Radioimmunoassay Measurement of Secretin Half-life in Man.
Gastroenterology. 1977; 72(1) 55-60.

This study used purified biological porcine secretin.

It was claimed that the mean fasting secretin concentration in 21 healthy volunteers was 69 ± pg/ml (22.6 pMol/L) (Range undetectable to 110 pg/ml).

The rate and duration of infusion was 9 CU/hr • kg^{-1} over 1 hour in 6 healthy male subjects. Reported clearance estimates were 540 ± 9.5 (SEM) ml/min. This is in the same range as in Stud. Plots of baseline corrected concentrations in 3 subjects indicate the end of infusion concentrations ranges from approximately 4 - 9 ng/ml. (1.3 to 3.0 nM/L).

The mean half-life (± SEM) reported in this study is 4.06 ± 0.82 minutes.

(3) Study 3

Christ A, Werth B, Hildebrand P, Gyr K, Stalder GA, and Beglinger C.
Human Secretin: Biological Effects and Plasma Kinetics in Humans.
Gastroenterology. 1988; 94(2) 311-316.

This study compared the pharmacokinetics and pharmacodynamics of synthetic porcine secretin (not [redacted] and synthetic human secretin in 6 healthy male volunteers (mean age 24 ± 1 year, mean weight 68 ± 2 kg).

Insufficient data were provided for the analytic method although it was claimed that the sensitivity was 0.8 ± 0.02 pMol/L and the intra-assay variability was <10% at 3.3 pMol/L.

Secretin pharmacokinetics was studied after a 15 second intravenous infusion of 125 ng/kg. This resulted in a biphasic concentration vs. time profile, with a mean increase in plasma secretin over baseline of approximately 2000 pMol/L. The elimination half-life of the first phase appears to be below 5 minutes with the second phase elimination half-life approximately 15 minutes. Data was not provided and these half-lives are estimated by the reviewer from a figure (See Figure 2). It was claimed that data from two of the 6 subjects best fit a one-compartment model, whereas the data from the other 4 subjects best fit a two-compartment model. The values for mean half-life (± SEM) that is given is based on a one-compartment model for all subjects (2.84 ± 0.62 min). The use of a one-compartment model is clearly inappropriate for some subjects, thus these values are inaccurate.

In addition to the rapid infusion over 15 seconds, three infusion rates administered over 45 minutes were also examined in this study. Mean clearance was reported as 14.8 ± 0.7 ml/min/kg. (Approximately 1036 ml/min/70 kg), however this may be an average clearance for all dose levels.

Clearances for each dose level were also estimated by this reviewer. It appears that secretin may have nonlinear kinetics at concentrations below those achieved with clinical use (0.2 µg/kg over 1 minute). It is possible that this apparent nonlinearity could be due to nonlinear binding of drug to the infusion apparatus.

Table 6 Estimated Clearances from Study 3

Dose of Secretin (ng/kg • hr^{-1}) over 45 minutes	Dose of Secretin (pMol/kg • hr^{-1}) over 45 minutes	Increment in Porcine Secretin Concentration over basal concentrations (pMol/L)	Estimated Clearance by OCPB Reviewer ml/min/70 kg
15.5	5.07	2.6 ± 0.9	2276
62.5	20.45	17.7 ± 2.7	1348
260	85.1	284.± 14.1	350

Figure 2 Porcine & Human Secretin Conc. vs. Time Profile after 125 ng/kg over 15 Seconds

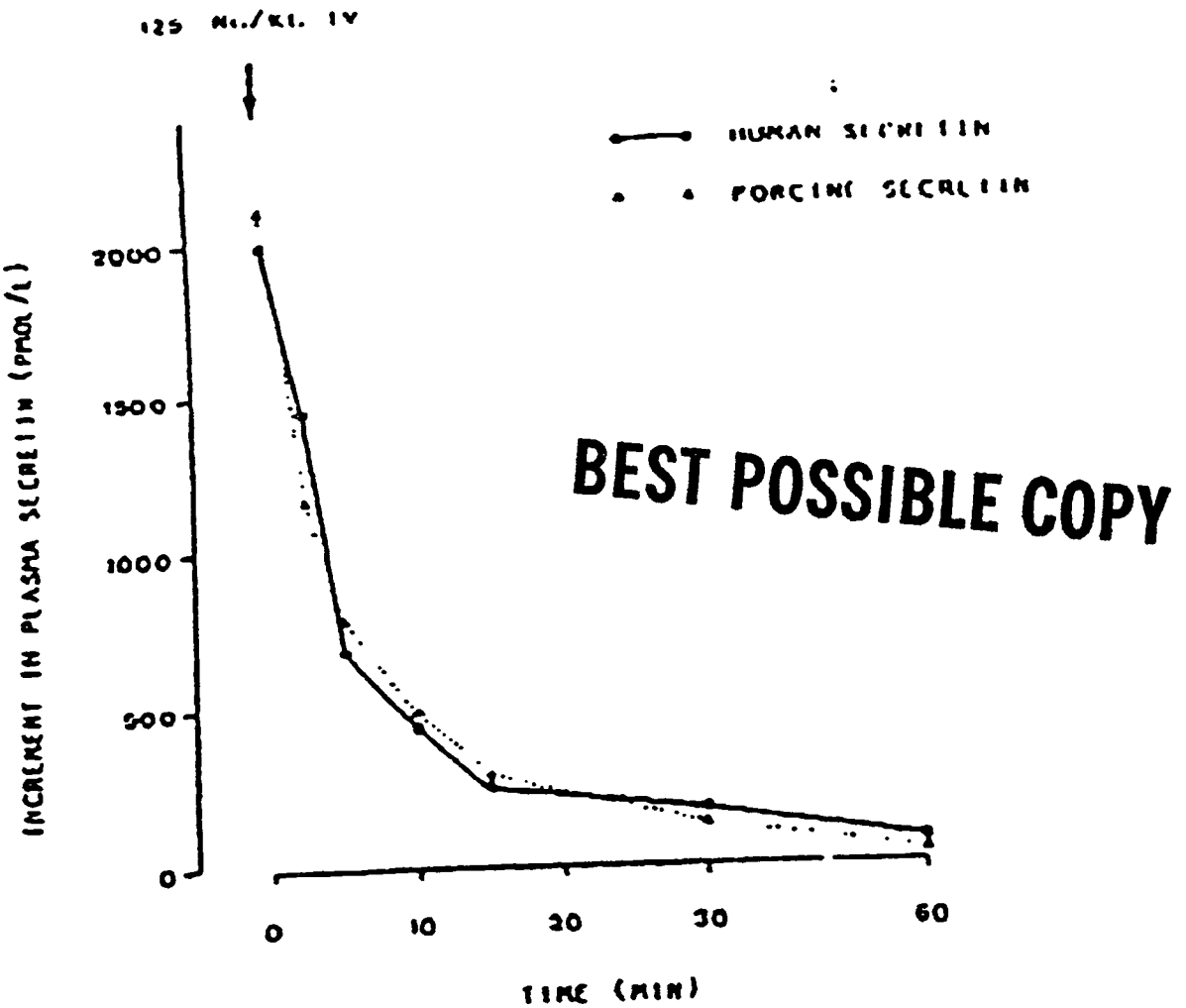


Figure 4. Disappearance of immunoreactive secretin after rapid intravenous bolus infusions of 125 ng/kg of synthetic porcine or synthetic human secretin in 6 healthy subjects. Points are mean values obtained after subtraction of basal values.

(4) Study 4

Carr-Locke DL, Gregg JA, and Chey WY.
Effects of Exogenous Secretin on Pancreatic and Biliary Ductal and Sphincteric Pressures in Man Demonstrated by Endoscopic Manometry and Correlation with Plasma Secretin Levels.
Digestive Diseases and Sciences. October 1985; 30(10) 909-917.

This study utilized synthetic secretin, although the type (i.e. species) was not specified, additional data from the sponsor obtained from the authors indicate that it was porcine secretin, however it is not

Twenty healthy volunteers, nine male 19-31 yo and eleven female 19-35 yo were studied in this study.

Synthetic secretin was used at a concentration of 125 ng/ml in 0.9% NaCl without added albumin.

.. Secretin infusate was sampled at beginning and end of infusion, and the calculated mean infusion rates based on the mean measured infusate concentrations are listed in Table 7 and are 49% to 53% of the expected infusion rate. However, it should be kept in mind that these are approximate concentrations since they are the mean of the infusate concentrations at the beginning and end of the infusion and the authors found decreasing infusate concentrations up to 2 hours.

Eight doses were infused sequentially for 15 minutes each, and steady-state was not achieved for any dosage within the 15 minute infusion period, which is inconsistent with the typically reported half-life of 2-4 minutes The reported results are listed in Table 7. Plasma concentrations achieved during the lowest four infusion rates were claimed to be within the concentration range achieved after a meal. The next highest dosage resulted in concentrations just slightly higher, and there was a non-linear increase in concentrations at the two highest doses.

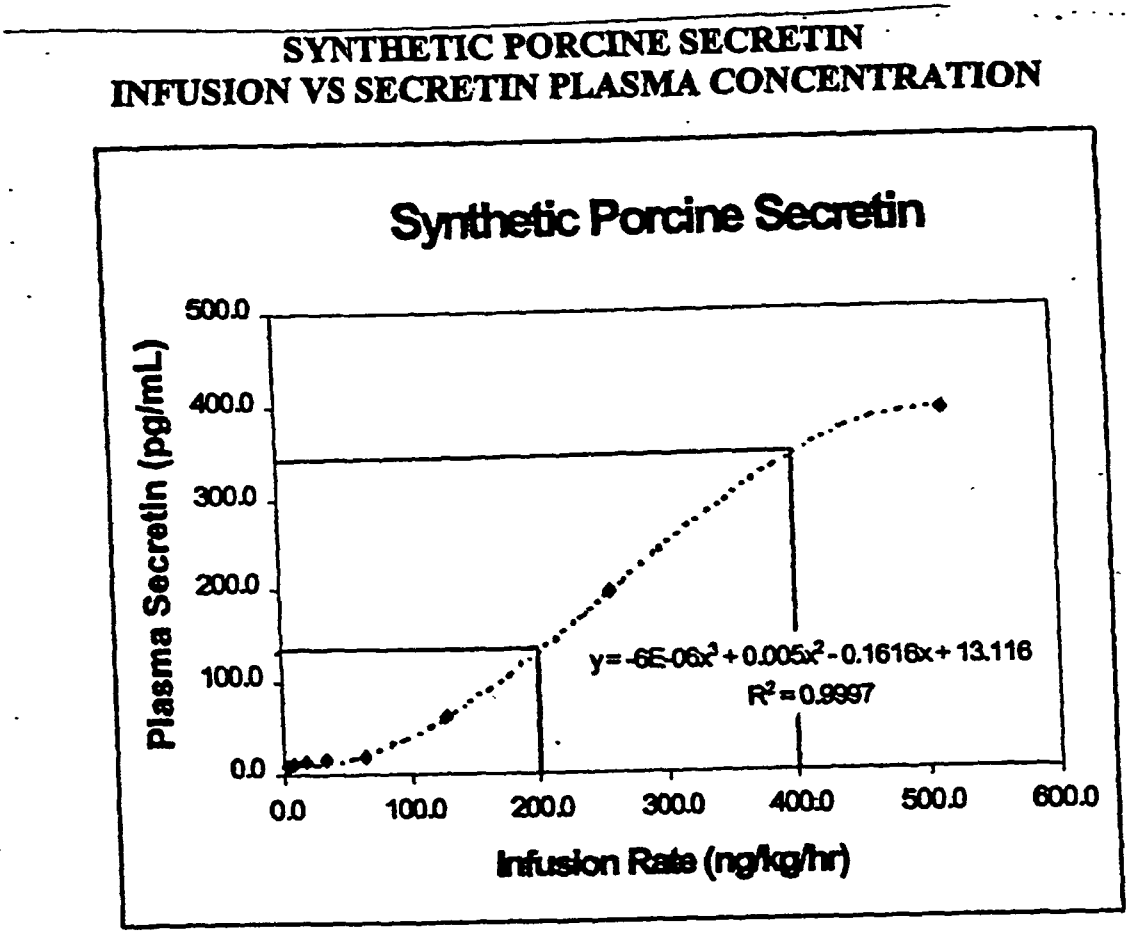
Table 7 Pharmacokinetic Metrics for 15 minute CIVI of Synthetic Secretin[a]

Dosage (ng/kg/hr)	Dosage (CU/kg/hr)[b]	Dosage Adjusted for Binding to Infusion Apparatus (ng/kg/hr)	Reported Plasma Secretin Concentrations (pg/ml)	Reported Clearance (ml/min)	Reported Clearance (ml/min/ 70 kg)	Estimated Clearance (ml/min/ 70 kg)	Estimated Clearance Adjusted for Potency (ml/min/ 70 kg)
Saline	0.0		8.5 ± 1.2	9.52	666.4	—	—
8.05	0.031	4.3	12.9	12.54	877.8	728	389
16.1	0.0625	8.6	14.4	19.66	1376.2	1304	697
32.2	0.125	16.9	16.0[c]	35.31	2471.7	2348	1232
64.4	0.25	33.2	19.7 ± 4.0	60.13	4209.1	3814	1966
129	0.5	65.6	61.3 ± 24.5	53.09	3716.3	2455	1249
258	1.0	129.2	195.8	33.45	2341.5	1537	770
516	2.0	252.2	391.1	29.31	2051.7	1539	752

a type of secretin unknown
b based on conversion of 1 mcg to 3.88-4.0 CU
c significantly different from basal

Mean plasma concentrations vs. dose are shown in Figure 3 and the nonlinearity is easily seen. In contrast to the nonlinearity at the low end, the nonlinearity observed in the figure at the high end might be spurious, due to fitting the data. Alternatively, it might be due to the concentrations being above the upper limit of the assay.

Figure 3 Synthetic Porcine Secretin (Non- — , Concentration vs. Dose



5. Special Populations

a) Chronic Renal Failure

The sponsor claimed that there were no data in any special populations. However, there were two literature citations in the references provided by the sponsor.

Rhodes et. al. Clin Ewa 1975 23:255A as cited in Kolts BE and McGuigan JE. Radioimmunoassay Measurement of Secretin Half-life in Man. Gastroenterology. 1977; 72(1) 55-60.

Rhodes et. al. Clin Ewa 1975 23:255A as cited in Chey WY and Chang TM.
Secretin Chapter 17 Handbook of Physiology - The Gastrointestinal System II. 359-402.

It was claimed in the first article that fasting serum secretin concentrations were elevated and half-life disappearances were prolonged in patients with chronic renal failure.

In the second article a figure was provided, that indicated that the half-life was approximately doubled from a mean of 2.39 minutes (n=8) to 5.95 minutes (n=7) in CRF (See Figure 4). Plasma secretin was from the figure.

Figure 4 Secretin Elimination in Chronic Renal Failure

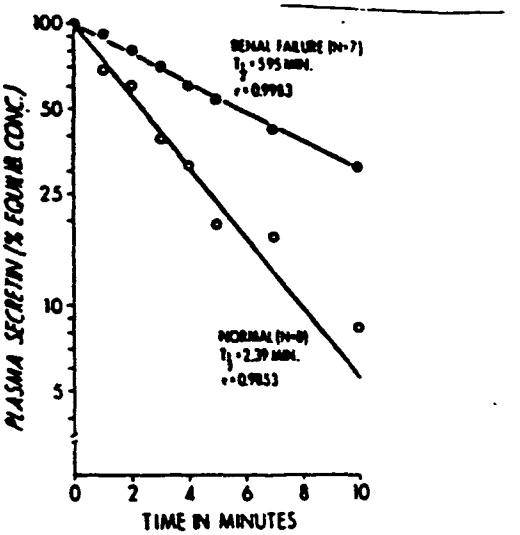


FIG. 19. Plasma half time of secretin determined immediately after 1-h intravenous infusion of secretin in 8 control subjects and in 7 patients with chronic renal failure. Equilibrium concentration equaled plasma secretin increment over basal at end of 1-h infusion. All values were normalized so that equilibrium concentration was 100% in each subject. Half times were calculated from elimination constants obtained by linear regression analysis of natural logarithms of mean normalized concentration versus time. [From Chey et al. (98).]

b) Hepatic Failure

See paragraph VII.2 Routes of Elimination on page 13.

6. Plasma Protein Binding

Protein binding data were reported in the following reference.

Burhol PG, Jenssen TG,, Florholmen J, and Jorde R. Protein-binding of Secretin in Human Plasma. Acta Physiol Scand 1985 123, 339-347.

However, it was not studied at clinically relevant concentrations.

Also, the type of secretin is not mentioned. The secretin appears to be sourced from Kabi Vitrum, Stockholm Sweden.

A radioimmunoassay was utilized but details and validation data was not provided.

Binding to plasma proteins was approximately 37% at concentrations up to 5.8 fMol/L at 20 °C. This corresponds to a mass concentration of 0.0177 pg/ml. This is well below the concentrations reported in the 3 published articles that were provided (approximate concentrations 50 pg/ml).

There appears to be at least two binding proteins albumin and another protein that was not identified.

Based upon the molar doses of secretin that will be administered i.e. 5 µg/100 kg or 1.64 nMoles / 100 kg it's highly unlikely that saturation of protein binding sites will occur, since total plasma protein far exceeds this amount.

B. Pharmacodynamics

1. Overview

Three original pharmacodynamic studies and two literature citations were submitted (See Table 8).

Table 8 Pharmacodynamic Studies

Protocol/ Study Number	Protocol Title / Literature Citation
CRC99-10	A Single Center Study Evaluating the Pharmacokinetic Profile of a Single Intravenous Dose of Synthetic Porcine and Synthetic Human Secretin in Normal Subjects.
CRC97-1	A Double Blind, Randomized, Four-Treatment, Latin Square Crossover, Pharmacodynamic, Dose-Response Study of Intravenously Administered Synthetic and Extracted Porcine Secretin for Use as a Diagnostic Agent to Evaluate Exocrine Pancreatic Function in Normal Healthy Subjects.
CRC98-1	A Randomized Crossover Study Evaluating Synthetic Porcine Secretin and Biologically Derived Secretin for the Assessment of Exocrine Pancreas Function in Patients with a Diagnosis of Chronic Pancreatitis.
Study 3	Christ A, Werth B, Hildebrand P, Gyr K, Stalder GA, and Beglinger C. Human Secretin: Biological Effects and Plasma Kinetics in Humans. Gastroenterology. 1988; 94(2) 311-316.
Study 4	Carr-Locke DL, Gregg JA, and Chey WY. Effects of Exogenous Secretin on Pancreatic and Biliary Ductal and Sphincteric Pressures in Man Demonstrated by Endoscopic Manometry and Correlation with Plasma Secretin Levels. Digestive Diseases and Sciences. October 1985; 30(10) 909-917.

21CFR§320.24(4) states that pharmacodynamic studies are sufficient for demonstrating bioavailability 'only when analytical methods cannot be developed'. Since, available information indicates that analytical methods can be developed the pharmacodynamic data cannot be considered an adequate substitute for bioavailability data.

2. — Effects on Gastrin Secretion

a) Study 99-10 - Effect on Gastrin Secretion in Normal Volunteers

An interim study report was submitted in late December 1999 (letter date December 29, 1999) for study 99-10 and a study synopsis was submitted 03 February 7, 2000. This study examines both PK and the PD effect on gastrin secretion. No pharmacokinetic data were submitted with either submission. However, the effect on gastrin concentrations with a 0.4 µg/kg dose was minimal. The observed mean change in gastrin concentration of approximately 10 pg/ml was not even close to the primary efficacy criteria of a change of 110 pg/ml.

3. — Effects on Pancreatic Secretion

a) Protocol CRC97-1 Comparative Pharmacodynamic Dose Response Study in Normal Subjects

This was a double-blinded, randomized, active controlled crossover study comparing 3 dosages of synthetic porcine secretin — to a 1 CU/kg dose of biologically derived porcine secretin.

Treatments:

Treatment 1	bPS	1.0	CU/kg over 1 minute	(1.0 CU / 0.1 ml 0.9% NaCl)
Treatment 1	sPS	0.05	µg/kg over 1 minute	(0.05 µg / 0.1 ml 0.9% NaCl)
Treatment 1	sPS	0.2	µg/kg over 1 minute	(0.2 µg / 0.1 ml 0.9% NaCl)
Treatment 1	sPS	0.4	µg/kg over 1 minute	(0.4 µg / 0.1 ml 0.9% NaCl)

Doses of sPS were chosen to equal 0.25, 1, or 2 CU/kg based upon *in vitro* assays of potency.

Each subject first received a test dose of 1 CU or 0.05, 0.2, or 0.4 µg

Interperiod washout: 1 week

Subjects:

There were 13 subjects. including 4 men and 9 women, mean age 28.9 years, mean height 101.1 cm, and mean weight 67.8 kg. Eleven were Caucasian, one Asian, and one Native American.

Pharmacodynamic Measures:

Volume, Bicarbonate Concentration [HCO_3^-], Total Bicarbonate

Sampling:

Baseline				
Period 1	-20	to	-10	minutes
Period 2	-10	to	0	minutes
Treatment				
Period 1	0	to	10	minutes
Period 2	10	to	20	minutes
Period 3	20	to	40	minutes
Period 4	40	to	60	minutes

Statistical Analysis:

One-way repeated measures ANOVA with 4 levels.

Reviewer's Comment: This is actually a test of differences and not a test of equivalence.

Results:

When the data are examined in total there are no consistent significant differences between the higher two dosages of sPS and the 1 CU dose of bPS. However, the data were quite variable. Based upon this and that the evaluation was to detect differences, equivalence cannot be concluded based on this analysis.

Comparison of the results of this study with results from the literature indicate that the dosages being compared may be too high to detect any inequivalence. It's possible that Emax is being achieved with the two higher doses of sPS and with the dose of bPS being used. Consequently, there may be no reliable way to determine the comparability of the pharmacodynamic effects with the current data. In addition, nonlinear kinetics may be playing a role at these concentrations. It's unlikely that an Emax model could be fit to these data. Since there are insufficient doses along the concentration effect curve, as 2 of the 3 doses appear to have achieved a maximum effect, and the 0.05 µg/kg dose achieves a near maximal effect.

b) Protocol CRC98-1 Comparative Study in Chronic Pancreatitis

It was suggested in the filing memo from OCPB that this study could be reviewed as a secondary pharmacodynamic study. Upon further examination it was decided not to review this study as a clinical pharmacology study, as it was a phase III comparative efficacy study and not a dose-response study.

This study evaluated the effect of 0.2 µg/kg sPS over 60 seconds (the recommended administration rate) on pancreatic juice volume, bicarbonate concentration and total bicarbonate over a 1 hour period compared to baseline. This study examined this response in normal subjects, subjects with chronic pancreatitis, and subjects who have recovered from chronic pancreatitis. This study may provide support for the use of secretin, as a diagnostic agent in chronic pancreatitis.

A review of an informal statistical consult, indicates the following:

- Subjects with chronic pancreatitis (n=8) had a decreased response to porcine secretin.
- The subjects studied who had a history of chronic pancreatitis (n=4) but who recovered, had a response to porcine secretin somewhere between normal controls and patients with chronic pancreatitis.
- There is wide variability in response to both sPS and bPS. Although the responses are not different between treatments, the wide variability, and small sample size, precludes a determination of equivalence.

Correlations between responses after dosing with sPS and bPS were performed, but statistical analysis on the degree of correlation was not. The scale on the graphical analysis is such that it precludes a visual comparison. The statistical reviewer suggests that there is a trend toward a lower response in all parameters with sPS. This is plausible, as some of the impurities in the bPS could prevent adsorption of the bPS to the syringe or administration apparatus, resulting in a greater dose. However, the results from protocol CRC97-1 indicate that maximum effect should be achieved with this dose, and this is inconsistent with a lesser response to sPS. Alternatively, some of the impurities in bPS could have some pharmacodynamic effect through an alternative mechanism. Finally, the difference in activity could be spurious. Without rigorous pharmacokinetic/pharmacodynamic studies it will likely be impossible to reach any firm conclusions regarding the comparative *in vivo* activity of bPS and sPS. Consequently, the acceptability of sPS should be based upon whether it provides an acceptable level of clinical performance and should not be based on equivalence to bPS.

4. Effect of Porcine Secretin on Pancreatic Enzyme Secretion in Normal Subjects

**Christ A, Werth B, Hildebrand P, Gyr K, Stalder GA, and Beglinger C.
Human Secretin: Biological Effects and Plasma Kinetics in Humans.
Gastroenterology. 1988; 94(2) 311-316.**

There was no effect of porcine secretin on lipase or trypsin, and no effect on amylase at continuous infusion doses below 260 ng/kg/hr. In addition, the amount of amylase was still increasing at end of each 45 minute infusion.

5. Effect of Porcine Secretin on Pancreatic and Biliary Duct Pressures

Carr-Locke DL, Gregg JA, and Chey WY.
Effects of Exogenous Secretin on Pancreatic and Biliary Ductal and Sphincteric Pressures in Man Demonstrated by Endoscopic Manometry and Correlation with Plasma Secretin Levels. Digestive Diseases and Sciences. October 1985; 30(10) 909-917.

Pancreatic Duct Sphincter Pressure	Statistically significant increase only at 2 highest infusion rates
Bile Duct Sphincter Pressure	No effect at any infusion rate
Duodenal Pressure	No effect at any infusion rate

VIII. LABELING

A detailed critique of the labeling was not performed due to the lack of adequate data.

Data on the pharmacokinetics of sPS may need to be incorporated into the labeling in the future, when it becomes available.

Information on the stability and handling of the drug product during and after reconstitution, and during administration needs to be incorporated into the labeling. Factors that need to be considered for inclusion in the labeling are the type of syringe and intravenous administration tubing, the length of tubing between the injection site and the body, temperature, and the time in each container/administration apparatus.

IX. COMMENTS FOR THE SPONSOR

A. Comments that should be addressed by the sponsor prior to approval

1) Data detailing the physical and chemical stability of — during and after reconstitution needs to be submitted. This needs to include evaluation of the degree adsorption of — versus time to the vial, syringes, and administration apparatus, under realistic conditions.

B. Comments that should be addressed by the sponsor when data from pending clinical/pharmacokinetic studies are submitted

1) Information on the reconstitution, handling and administration of — needs to be provided for any clinical pharmacology and clinical pharmacokinetic studies.

2) The sponsor is reminded that stability information on — is expected to be included with the assay validation data.

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ON ORIGINAL

X. SIGNATURES

(S)

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Feb 10, 2000
Date

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

(S)

FD - Suresh Doddapaneni, Ph.D., Team Leader

2/10/00
Date

OCPB Briefing Meeting: Wednesday February 9, 2000 10:00 AM PKLN 13B45

Attendees: Goldkind, Aurrechio, Gallo-Torres, Lazor, Metz, LeeP, Huang, Hunt, Doddapaneni, Kavanagh R

CC: NDA 21-209 (orig., 1 copy)
HFD-180 (Goldkind, Talarico, Aurrechia, WJ Chen, Strongin)
HFD-850 (Lesko)
HFD-870 (M Chen, Huang, Doddapaneni, Kavanagh, LeeD)
HFD-340 (Vish)
Central Document Room (Barbara Murphy)

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APPENDIX 1 - PK Summary Tables

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Table 9 Subject Characteristics in Literature Citations

Reference	n	Subjects	Age	Weight
You et al. 1983	30	Healthy subjects	—	—
Kolts and McGuigan Gastroenterology 1977	6	—	—	—
Christ et al. Gastroenterology 1988	6	Healthy males No history of GI disorders	24 ±1	68 ± 2 kg
Carr-Locke et al. Dig Dis Sci 1985	20	9 Male / 11 Female	M 19-31 yo F 19-35 yo	—

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Table 10 Summary of Pharmacokinetic Data

Reference	Type of Secretin	Administration	n	t1/2 (minutes)	Clearance	Cpss	Comments
You et al. 1983	GIH Secretin	0.03 CU/kg/hr x 1 hour	30	No decline at 15 minutes after the end of the infusion	Not Determined 817 to 1089 ml/min/70 kg estimated	approximately 10 -12 pg/ml	Type of secretin not mentioned. May be different species. Mean plasma concentrations
Kolts and McGuigan Gastroenterol 1977	Purified bPS	9 CU/kg/hr x 1 hour	6	4.06 ± 0.82 min (± SEM)	540 ± 9.5 ml/min (mean ± SEM)	4 - 9 ng/ml	Not Stated how clearance was calculated.
Christ et al. Gastroenterol 1988	sPS Not [illegible]	125 ng/kg over 15 seconds	6	2.84 ± 0.62	1036 ml/min/70 kg (14.8 ± 0.7 ml/min in sponsor's summary. This is equivalent to approximately 1036 ml/min/70 kg)	Cmax 2000 pMol/L	t1/2 based on one-compartment model. This is not appropriate for all subjects
		15.5 ng/kg/hr x 0.75 hour			2276 ml/min/70 kg	↑ 2.6 ± 0.9 pMol/L	Cl estimated by reviewer Cpss increase over baseline
		62.5 ng/kg/hr x 0.75 hour			1348 ml/min/70 kg	↑ 17.7 ± 2.7 pMol/L	Cl estimated by reviewer Cpss increase over baseline
		15.5 ng/kg/hr x 0.75 hour			350 ml/min/70 kg	↑ 284 14.1 pMol/L	Cl estimated by reviewer Cpss increase over baseline
Carr-Locke et al. Dig Dis Sci 1985	Synthetic Secretin 125 ng/ml in NaCl w/o albumin	3.0 ng/kg/hr x 0.25 hour	20	Not Reported	9.52 ml/min	8.5 pg/ml	Formula given is incorrect
		8.1 ng/kg/hr x 0.25 hour			12.54 ml/min	12.9 pg/ml	
		16.1 ng/kg/hr x 0.25 hour			19.66 ml/min	14.4 pg/ml	
		32.2 ng/kg/hr x 0.25 hour			35.31 ml/min	16.0 pg/ml	
		64.4 ng/kg/hr x 0.25 hour			60.13 ml/min	19.7 pg/ml	
		129.0 ng/kg/hr x 0.25 hour			53.09 ml/min	61.3 pg/ml	
		258.0 ng/kg/hr x 0.25 hour			33.45 ml/min	195.8 pg/ml	
		516.0 ng/kg/hr x 0.25 hour			29.31 ml/min	391.1 pg/ml	