CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

MEDICAL REVIEW(S)

2-5-02

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 21-209
SUBMISSION DATE: August 17, 1999
APPROVABLE LETTER: November 28, 2000
AMENDMENT TO NDA 21-209 (ANSWER TO NOVEMBER 28, 2000 LETTER): September 17, 2001
APPLICANT: ChiRhoClin Inc
DRUG: Synthetic Porcine Secretin (sPS)
PHARMACOLOGY CATEGORY: GI hormone/pancreatic polypeptide secretagogue
PROPOSED INDICATIONS: 1) Diagnosis of pancreatic exocrine —
2)
3) Diagnosis of gastrinoma ;
4) Facilitation of during ERCP
DOSAGE FORMS AND ROUTE OF ADMINISTRATION: Intravenous, 0.2 µg/kg and 0.4 µg/kg over one minute
MEDICAL REVIEWER: Marcelo A. Barreiro, MD, MSc
MATERIAL CONSIDERED: 1) MO's Reviews of February 2000, Gastrinoma Indication; March 2000, Diagnosis of Pancreatic Exocrine Dysfunction —, Larry Goldkind, MD; 2) Response to approvable letter dated May 16, 2000, Scheldon Kress, MD; 3) Amendment to NDA # 21-209, dated 17 September, 2001.

EXECUTIVE SUMMARY

A total of 920 patients have been studied until 17 September 2001. Of these, 556 received sPS, 15 received bPS and 364 received placebo. There were 41 adverse events in 40 patients. There were no serious adverse events. At doses of 0.2 µg/kg and 0.4 µg/kg, administered intravenously over one minute, in single doses for testing procedures, sPS is a safe and well tolerated drug.

UPDATED SAFETY REVIEW

INTRODUCTION

ChiRhoClin submitted an NDA for synthetic porcine secretin on May 14,1999 (#21-136).. This NDA was divided into 2 NDAs in October, 1999. NDA #21-136 covered CMC, Microbiology, Pharm/Tox, Biopharmaceutics and the Clinical indications of exocrine pancreas function testing and —. NDA #21-209 was created as an administrative mechanism to accept the diagnosis of gastrinoma indication for filing and contains only clinical data related to that indication with a Right of Reference to NDA #21-136.

On March 24, 2000, ChiRhoClin received an approvable letter for the exocrine pancreas function testing indication of NDA #21-136. Complete responses to the outstanding questions in the letter were submitted on May 8, 2000.

IND #54-196 relates to the development program for synthetic porcine secretin (sPS) for diagnostic indications. This program is completed. NDA #21-136 was filed in May, 1999. Approvable letters were received in March, 2000 for the exocrine pancreas function indication, in May, 2000 for gastrinoma, and again in September, 2000 for both. Items requiring further responses were confined to the CMC section.

During this reporting period (March 2000 - March 2001) six studies were conducted under this IND. CRC97-2 amendment was a randomized, placebo controlled crossover study for use of sPS to facilitate cannulation of the minor papilla in patients with pancreas divisum during ERCP. This study is completed. The second study is CRC97-2, which is the original open-label study. This trial enrolled 15 patients since the last report and is now closed. The third study is CRCOO-3, which is the Treatment Protocol authorized by FDA in October, 2000, which serves as the replacement study for 97-2. The fourth study is CRC97-3 for prevention of post-ERCP pancreatitis. This study has been active since May, 1998. The fifth study is CRC99-8, a 3-way crossover study in 6 patients with a tissue diagnosis of gastrinoma. The sixth study is CRC99-9, a 3-way crossover study evaluating exocrine pancreas function. CRC99-8 and CRC99-9 are also complete and closed.

SAFETY RESULTS

- Integrating the safety results of these six studies, there were 41 adverse events in 40 patients among a total of 920 patients evaluated.
- There were no serious adverse events.
- Table one below lists the adverse events for sPS and bPS since the inception of the program.

TABLE 1

ADVERSE EVENTS

Event	sPS N = 556 Incidence (Patients)	bPS N = 15 Incidence (Patients)	Placebo N = 364 Incidence (Patients)
Abdominal cramps	1 (1)	0	0
Abdominal discomfort	6 (5)	2 (2)	0
Bleeding – sphincterectomy	2 (2)	0	1 (1)
Bleeding – upper GI 2° to endoscopic abrasion	1 (1)	0	1 (1)
Bloating	1 (1)	0	0
Bradycardia (mild)	2 (2)	0	0
Decreased blood pressure	2 (2)	0	1 (1)
Diaphoresis	2 (2)	0	0
Diarrhea	1 (1)	0	0
Endoscopic perforation of pancreatic duct	2 (2)	0	0
Fatigue	0	0	1 (1)
Fever	1 (1)	0	0
Flushing	0	1 (1)	0
Leukocytoblastic vasculitis	0	0	1 (1)
Nausea	5 (5)	1 (1)	0
Rash-abdomen	0	0	1 (1)
Transient low O_2 saturation	1 (1)	0	0
Transient respiratory distress	1 (1)	0	0
Urticaria 2° contrast material (prior to secretin administration)	1 (1)	0	0
Vomiting	1 (1)	0	0
Warm sensation in face	0	1 (1)	0
Total pts. with AEs (%)	29 (5.2)	5 (33.3)	6 (1.6)

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/s/

Marcelo Barreiro
1/28/02 12:14:27 PM
MEDICAL OFFICER

Hugo Gallo Torres
2/5/02 04:59:02 PM
MEDICAL OFFICER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 21-209

Applicant: ChiRhoClin Inc.

Drug: Synthetic Porcine Secretin (SPS)

Indication: 1. Diagnosis of Pancreatic exocrine –
2

3. Diagnosis of gastrinoma –
4. Facilitation of – during ERCP

Submitted: Response to approvable letter dated May 16, 2000

Medical Reviewer: Scheldon Kress, M.D.

Material Reviewed: Response to approvable letter dated May 16, 2000 which required submission of the following additional information (copy of approvable letter is in Appendix 1): The reply submission dated May 26, 2000 was received on May 30, 2000 and contained the following information.

1. *All information, including identification, case report forms, and primary source documents for subjects number 5 and number 6 in the study report entitled, "A Randomized, Controlled, Crossover Study Evaluating Synthetic Porcine Secretin, Synthetic Human Secretin, and Biologically Derived Porcine Secretin for the Diagnosis of Gastrinoma Pooled analysis of CRC 99-8 and CRC 97-2 (with 2-Way Crossover Amendment) studies", submitted April 14, 2000.*

Response: Sponsor provided CRFs for all <u>six</u> patients that participated in study CRC99-8. The patient numbers and subject randomization numbers were different thus leading to some confusion:

Patient Numbers	Randomization Numbers	Subjects
01	# 6	
02	# 5	
03	# 2	
04	# 3	
05	# 1	
07	# ?	

2. *identification of the assays for serum gastrin used in the database including the apparent outside laboratory associated with subject #3 — from Study CRC 97-2*

Response: The serum gastrin concentrations for CRC97-2 (2-way amendment) were determined by the laboratory at — This study contributed three patients that were pooled with the Metz study CRC99-8. The sponsor provided the laboratory procedures for assay of serum gastrin along with their supporting publications. The laboratory confirmed the performance of simultaneous secretin and gastrin radioimmunoassays on three patients, each sample assayed in triplicate.

The serum gastrin concentrations for the Metz study CRC99-8 were done at — using a commercial assay kit manufactured by — The laboratories' procedure and a copy of the manufacturer's brochure of the gastrin assay kit is also provided.

Under 21 CFR 314.50(d)(S)(vi)(b), the Agency requested that you update your NDA by submitting all safety information you now have regarding your new drug Also, provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. *Retabulation of all safety data, including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission.*
   Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

Response: There were 3 AEs in CRC97-1 in one of the 12 normal volunteers. These were transient, mild flushing lasting 5 minutes, resolving spontaneously, and probably related to test drug which occurred with sPS (synthetic Porcine Secretin) at the 0.2 and 0.4 µg/kg doses and with bPS (biologically derived Porcine Secretin) at the 1 CU/kg dose.

In the second clinical study in normal subjects, CRC99-10 (pharmacokinetics), 4 of 13 subjects had 12 adverse events. During treatment Period A (sPS), four subjects had 12 AEs. One subject (#13) had 4 AEs as a result of the IV infiltrating prior to and during the administration of sPS. The subject received only a fractional dose of sPS, subcutaneously. The four AEs were mild to moderate in severity, lasted only a few

minutes, resolved without specific treatment and were rated as having an unlikely relationship to study drug. These AEs included lightheadedness, diaphoresis, thready pulse and hypotension.

The other 3 subjects (#1, 3, and 9) had 8 AEs including headache, nausea, lightheadedness, numbness and tingling in the left hand, pallor, diaphoresis and hypotension. All AEs were mild and 6 of the 8 were rated as having an unlikely relationship to the test drug while 2 had a possible relationship. The AEs lasted 10 to 75 minutes and resolved without specific treatment.

A listing of all AEs follows.

ADVERSE EVENTS IN STUDY CRC99-10

Sub #	Period	TRT	Event	Onset Time	End Time	Continuing	Severity	Relationship to Study Drug	Action	Outcome
1	1	A[1]	Headache	11 15	12 30	—	Mild	Possible	None	Resolved
3	1	A	Nausea	11 00	12 00	—	Mild	Possible	None	Resolved
3	1	A	Numbness left hand and fingers	11 00	12 00	—	Mild	Unlikely	None	Resolved
3	1	A	Tingling left hand and fingers	11:00	12 00	—	Mild	Unlikely	None	Resolved
9	1	A	Lightheadedness	11 10	11.20	—	Mild	Unlikely	Placed in recumbent position, cool cloth to forehead.	Resolved
9	1	A	Pallor	11 10	11.20	—	Mild	Unlikely	Placed in recumbent position, cool cloth to forehead.	Resolved
9	1	A	Diaphoresis	11 10	11.20	—	Mild	Unlikely	Placed in recumbent position, cool cloth to forehead.	Resolved
9	1	A	Hypotension	11.10	11.20	—	Mild	Unlikely	Placed in recumbent position, cool cloth to forehead.	Resolved
13[2]	1	A	Lightheaded	11.05	11.19	—	Moderate	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Diaphoresis	11:05	11.19	—	Moderate	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Thready Pulse	11:05	11.24	—	Moderate	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Lightheaded	11:19	11:24	—	Mild	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Diaphoresis	11:19	11:24	—	Mild	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Hypotensive	11:05	11:14	—	Moderate	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Hypotensive	11:14	11:19	—	Mild	Unlikely	Trendelenberg, cool cloth applied	Resolved

1 - TRT A = sPS

2 – Subject number thirteen was felt by the principle investigator to have had a vasovagal reaction to the IV itself which infiltrated and only gave a fractional dose of sPS subcutaneously

Six clinical studies with sPS in patients have been conducted. These are: CRC97-2 (open-label - 114 patients), CRC97-3 (ERCP pancreatitis - 375 patients randomized to sPS and placebo), CRC98-1 (crossover sPS and bPS - 12 patients), CRC98-2 (crossover sPS and sHS (synthetic Human Secretin) - 12 patients), CRC99-8 (3-way crossover, sPS, sHS, bPS - 5 patients), and CRC99-9 (3-way crossover, sPS, sHS, bPS - 3 patients to date).

Integrating the safety results of these 6 studies, there were 28 adverse events in 21 patients among a total of 540 patients evaluated. These appear in the table below.

ADVERSE EVENTS

Event	sPS N = 333 Incidence (Patients)	bPS N = 20 Incidence (Patients)	Placebo N = 187 Incidence (Patients)
Abdominal discomfort	5 (5)	1 (1)	0
Abdominal cramps	1 (1)	0	0
Diarrhea	1 (1)	0	0
Nausea	5 (5)	1 (1)	0
Decreased blood pressure	1 (1)	0	0
Headache	1 (1)	0	0
Endoscopic perforation of pancreatic duct	2 (2)	0	0
Fever	2 (2)	0	0
Slight upper GI bleed 2° to endoscopic abrasion	1 (1)	0	0
Urticaria 2° contrast material (prior to secretin administration)	1 (1)	0	0
Leukocytoblastic vasculitis	0	0	1 (1)
Diaphoresis	2 (2)	0	0
Hematoma	0	1 (1)	0
Flushing	0	1 (1)	0
Bradycardia (mild, few seconds)	1 (1)	0	0

There were no safety problems associated with study drug in these six studies.

There were 3 AEs in CRC97-1 in one of the 12 normal volunteers. These were transient, mild flushing lasting 5 minutes, resolving spontaneously, and probably related to test drug which occurred with sPS at the 0.2 and 0.4 µg/kg doses and with bPS at the 1 CU/kg dose.

Integrating the safety results of the four studies in patients, there were 15 adverse events in 12 patients among a total of 274 patients evaluated. These appear in the table that follows.

ADVERSE EVENTS

Event	sPS N = 157 Incidence (Patients)	bPS N = 12 Incidence (Patients)	Placebo N = 117 Incidence (Patients)	sHS N = 9 Incidence (Patients)
Abdominal discomfort	2 (2)	0	0	0
Abdominal cramps	1 (1)	0	0	0
Diarrhea	1 (1)	0	0	0
Nausea	1 (1)	0	0	0
Decreased blood pressure	1 (1)	0	0	0
Headache	1 (1)	0	0	0
Endoscopic perforation of pancreatic duct	2 (2)	0	0	0
Fever	1 (1)	0	0	0
Slight upper GI bleed 2° to endoscopic abrasion	1 (1)	0	0	0
Urticaria 2° contrast material (prior to secretin administration)	1 (1)	0	0	0
Leukocytoblastic vasculitis	0	0	1 (1)	0
Diaphoresis	1 (1)	0	0	0
Hematoma	0	1 (1)	0	0

There were no other safety problems associated with study drug in these four studies.

2. *Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.*

Response: There were only two dropouts in the entire clinical program. One was a normal subject in CRC97-1 who did not tolerate passage of the Dreiling tube and was discontinued after receiving bPS during Period 1. This subject never received sPS. The second was a normal subject in CRC99-10 whose IV infiltrated after receiving a fractional subcutaneous dose of sPS and who had a vasovagal reaction secondary to the infiltration.

3. *Details of any significant changes or findings.*

Response: There were no significant changes or findings related to safety since the original NDA #21-136 submission. Several NDA amendments have been filed since May, 1999 including the final study reports for CRC98-2 (Sept. 1999) and CRC99-10 (April *2000),* updated interim reports for CRC97-2 (open-label) and CRC97-3 (ERCP pancreatitis) (Dec. 1999), and interim reports for CRC99-8 (gastrinoma) (03/31/000 and 04/10/00) and CRC99-9 (April 2000).

4. Summary of worldwide experience on the safety of this drug.

Response: there have been no clinical studies using [redacted] outside the U.S. The drug has not been marketed in any territory.

5. Case report forms for each patient who died during a clinical trial or who did not complete a study because of an adverse event.

Response: There were no deaths for sPS in the clinical program. The one adverse dropout, which was in a normal subject in CRC99-10, as described in response 2.

6. English translations of any approved foreign labeling not previously submitted

Response: There is no approved or pending foreign labeling for this drug.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Response: There is no information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Reviewer's Comments:

ChiRhoClin Inc has provided satisfactory responses to the request for additional clinical information in the approvable letter dated May 16, 2000.

Recommendations for Regulatory Action:

1. **Approvability remains subject to resolution of the outstanding chemistry, manufacturing, and control deficiencies in NDA 21-136.**

2. **Based on the satisfactory responses to the request for additional clinical information, I recommend that Secretin be approvable for the diagnosis of gastrinoma**

Scheldon Kress, M.D.

November 27, 2000

cc:
NDA 21-209
IND
HFD-180/Division File
HFD-180/L Talarico
HFD-180/H Gallo-Torres
HFD-180/M Avigan
HFD-180/S Kress
HFD-181/P Levine
HFD-180/JChoudary
HFD-180/LZhou
f/t 11/28/00 jgw
N/21209011.0SK

APPEARS THIS WAY
ON ORIGINAL

JUN 16 2000

Division of Gastrointestinal and Coagulation Drug Products
Medical Officer's Review

NDA # 21-209

Submission Date: August 19, 1999
Filing over protest date: October 16, 1999

Generic name: Synthetic porcine secretin (SPS)

Proposed trade name: —

Sponsor: ChiRhoClin

Pharmacologic category: GI hormone/ pancreatic polypeptide secretagogue

Proposed indications: Diagnosis of — (gastrinoma)

Dosage forms and route of administration: Intravenous 0.4 micrograms/kg over one minute

Related NDAs: 18-290 approved 1981 Ferring biologic porcine secretin
21-136

Submissions reviewed:
1. Submission date August 17, 1999
2. Submission date February 3, 2000
3. Submission date February 18, 2000
4. Submission date March 8, 2000
5. Submission date March 16, 2000
6. Submission date March 31, 2000
7. Submission date April 14, 2000

Reviewer: Lawrence Goldkind, M.D.

Table of Contents

1. Background:

The sponsor submitted the original NDA 21,136 for this product on May 14, 1999. Four indications were proposed:

- For diagnosis of pancreatic exocrine function
- [redacted]
- Diagnosis of gastrinoma
- Facilitation [redacted] during ERCP

There were no controlled data on the last two indications and ***no subjects with Zollinger-Ellison Syndrome had received SPS in the entire database***. Thus, these two indications were not filed in view of the lack of clinical data to review. The sponsor was informed of the decision to file only the first two indications at a meeting with the division on September 14, 1999. The lack of controlled data was discussed and the sponsor was informed that independent diagnostic accuracy data or pharmacodynamic comparability to the approved Ferring secretin in the setting of gastrinoma diagnosis would be needed to adequately label SPS. ChiRoClin was also told that the impurities in the Ferring product might constitute bioactive peptides in the secretin stimulation test, thereby potentially affecting the optimal dose of secretin to be used diagnostically and the diagnostic range of the SST.

Literature review on the diagnostic range of the post-SST serum gastrin levels was the basis of approval for the Ferring secretin in 1981. The literature referenced for approval included the Ferring secretin and was therefore adequate to derive a dynamic range and diagnostic range for the test. Peptide purity has been addressed in the medical literature as an important factor in the diagnostic accuracy of various secretin-containing preparations. Differences in purity between the Ferring secretin and Boots secretin, another biologically derived product, have been addressed in the medical literature.[1] The issue of purity is important in any product, synthetic or biologically derived. In addition however the ***absence*** of potentially bioactive impurities that may impact on healthy and diagnostic ranges, sensitivity, specificity and proper dose of product are uniquely applicable to the current submission.

The proposed SPS has no published literature upon which to draw such support. The clinical relevance of this point was highlighted in an article by McGuigan and Wolfe published in Gastroenterology [79:1324-1331 (1980)].

"At the present time there is insufficient information in the literature to compare secretin provocation results using the several available forms of synthetic secretin with the results using the purified naturally occurring porcine secretins."[1]

During the September 14, 1999 meeting with the Division, the sponsor agreed to conduct a controlled study of patients clinically presenting for diagnosis. The size of the study was not agreed upon. It was understood that the small number of patients available for study with gastrinoma would preclude a trial with the power to assess specificity, sensitivity, accuracy, and predictive value in a statistical fashion. Thus the Division

agreed to preliminarily assess results in a small number of subjects (6 to 12 patients). The information in the September 14th, 1999 meeting supplemented advice given by the Division to the sponsor at a pre-NDA meeting on November 18, 1998. A reproduced section from the meeting minutes appears below.

> *The clinical program for synthetic porcine secretin consists of the volunteer subject study (CRC97-1), the chronic pancreatitis patient study (CRC98-1), and the ERCP study (CRC97-3) for additional safety data.*
>
> *ChiRhoClin believes these studies establish the diagnostic efficacy, safety and dosing guidelines for synthetic porcine secretin for the diagnostic indications and with the published literature on porcine secretin, which provided the basis for approval of the biologically derived drug, fully satisfy the requirements for NDA approval. Does the FDA concur with this assessment?*
>
> Any decision regarding the approvability of an application is based on the data for your product submitted in the NDA. It is premature at this time to make any conclusions regarding approvability. Since efficacy for the proposed NDA is to be supported by a small database consisting of only 24 patients in two studies, it is possible that more support may be needed. It may be necessary to submit clinical data, including data regarding the sensitivity and specificity, in support of the efficacy of your product for each requested indication. If literature is provided in support of efficacy, it must be from studies using your product or bioequivalence between the product used and your product must be demonstrated. Source documents from the referenced studies must be provided as well.
>
> Literature for studies utilizing the porcine derived product may be submitted as background information, but cannot serve as the basis for approval.

Despite the meeting of September 14, 1999, the sponsor chose to file over protest and the current NDA 21,209 was filed separately from NDA 21,136. This administrative separation of the gastrinoma indication from the other indications was due to the ***priority status*** required for a review of an NDA for a diagnostic that was proposed to be superior to available diagnostic modalities for a serious and life threatening disease.

1.1 Clinical Background

In 1902 Bayliss and Starling first showed that an extract from the gastrointestinal mucosa of pigs could stimulate pancreatic secretion in dogs. This was one of the earliest experiments documenting the generic concept of "hormonal" action. In 1962 purification of this porcine intestinal mucosal extract led to the sequencing of the 27 amino acid hormone, secretin. The carboxy-terminal is amidated. There is significant structural homology with other digestive hormones including vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP) growth hormone releasing factor and glucagon. This homology is preserved across species including human, bovine, porcine and canine. There is a 2 amino acid difference between the human and bovine sequences of secretin at amino acid position 15 and 16. Aspartamine and serine in the

porcine molecule at these positions is replaced with glutamine and glycine in the human molecule.

The homology among multiple digestive hormones has made it difficult to precisely pinpoint the sites of secretin synthesis as well as secretin receptor distribution within the body. There are conflicting data regarding the presence of secretin activity in the central nervous system. RNA blot hybridization using tissue from the rat has indicated that the small intestine is the major site of secretin gene expression in this species. Secretin levels were highest in the ileum. Secretin RNA was below the level of detection in the stomach, cerebral cortex brainstem, hypothalamus, pituitary, and adult pancreas. Other studies using oligonucleotide primers for rat secretin, amplification of first strand cDNA suggested that secretin may be present at low levels in cerebral cortex, brainstem and hypothalamus. Other amplification studies in animals have suggested the presence of secretin in brain, kidney, heart and testis. These extremely sensitive methods of localization however, may be overly sensitive and produce artifactual results. The presence and potential role of secretin in these extraintestinal sites require further study and clarification.

Biological role of secretin:
Luminal stimulants to secretin release include gastric acid, bile salts, peptides, and long chain fatty acids. Cholinergic and adrenergic stimuli do not influence the luminal contents stimulatory effects on secretin release. Starch does not appear to be a trigger for secretin release.
Table 1 displays the known effects of secretin. Not all are felt to be clinically relevant.

Table 1

	Secretin
Water-electrolyte secretion	
Stomach acid	*−
Pancreas	*+
Liver	+
Brunner's glands	+
Enzyme secretion	
Stomach	+
Pancreas	±
Intestine	+
Endocrine secretion	
Gastrin	*−
Insulin	+
Glucagon	±
Somatostatin	+
Smooth muscle	
Lower esophageal sphincter	−
Stomach	−
Intestine	−
Colon	−
Gallbladder	+
Sphincter of Oddi	−
Growth	
Gastric mucosa	−
Pancreas	±
Metabolic	
Lipolysis	+
Glycogenesis	
Cardiovascular system	
Heart rate	+
Stroke volume	+
Blood flow	
Superior mesenteric artery	+
Hepatic artery	−
Pancreatic artery	+
Small intestinal artery	+
Gastric mucosal artery	−
Femoral mucosal artery	+

*, Physiological action; +, stimulation; −, inhibition; ±, inconclusive; 0, no response.

The effects in Table 1 include those identified in animal models and not necessarily clinically relevant effects. ***The safety data to be discussed in NDA 21,136 and this review may potentially be related to the cardiovascular effects of increased blood flow, especially mesenteric blood flow. Vasodilatation, hypotension, diaphoresis and abdominal cramps may conceivably be secondary to this preclinical finding noted in Table 1. This suggestion is strictly speculative.***

Pharmacological uses for secretin have been investigated for over three decades since purified secretin became available. The Karolinska Instituet in Stockholm produced the most highly purified form in the 1970s. Manufacture of the product was transferred to Kabi Diagnostica in 1977. In 1981 the United States FDA approved Secretin-Kabi. It is derived from porcine tissue extract. It is indicated for the:

1.diagnosis of pancreatic exocrine function
2. as an adjunct in obtaining desquamated pancreatic cells for cytopathologic examination
3. Diagnosis of gastrinoma (Zollinger-Ellison syndrome/ZE)

Ferring assumed production and marketing in 1989. As mentioned above, as of June 1999 Ferring has ceased production of their biologic secretin product.

1.3 Important information from related NDAs

The FDA approval of the marketing of Secretin –Kabi was based on published literature review. The basis for approval of that biologically derived product in 1981 is summarized below.

A literature review was the basis for approving Secretin-Ferring for this indication. There was no question that the biologic phenomenon of a dramatic rise in serum gastrin level in response to an infusion of secretin is unique and typically seen in patients with ZE. The differential diagnosis for this type of response in serum gastrin level following infusion of secretin is limited to ZE. ***For this reason, this reviewer does not feel that data were necessary to prove that SPS had the same discriminating ability between gastrinoma and other causes of elevated fasting unstimulated serum gastrin levels such as achlorhydria, chronic renal failure and G-cell hyperplasia.*** Diagnostic differentiation between gastrinoma and other causes of elevated fasting gastrin concentrations may be extrapolated from evidence supporting the differentiation between gastrinoma and non-gastrinoma (healthy) subjects in the current database supported by medical literature using biologically derived secretin. The issues of potency of effect and bioactivity of impurities in the Ferring BPS product that are central to this NDA are not materially related to the intrinsic biological effect of secretin on gastrin producing tumors.
In the advisory committee and again in the review by Dr. Garvey the relevant issue was defining the diagnostic criteria or cutoff for ZE.

Five studies submitted in the NDA were considered in Dr. Garvey's review medical officers review dated February 4, 1981. The studies used various diagnostic criteria for ZE as well as varying dosages and products (Boots and GIH). Among healthy subjects 0/46 showed a rise in gastrin of 110 pg/ml or greater. Among patients with duodenal ulcer but no suspicion of ZE 0/49 had a diagnostic rise in gastrin.

Among patients with "proven" ZE (histology or persistently elevated gastrin s/p gastrectomy) 37/37 had a positive secretin test.

In the gray zone of suspected but unconfirmed cases of ZE the data were not clear.
The reviewer concluded that:

"The data from the five studies summarized above provide substantial evidence that assessment of GIH (Kabi product) secretin stimulated serum gastrin response in *patients with suspected gastrinoma is a powerful diagnostic technique. Using 2 CU/kg of secretin and an antibody for the gastrin RIA similar or identical to that prepared by Rehfeld and used by Deveny et al, Lamer et al. and Mihas et al. an increment in fasting gastrin of 110 or more pg/ml above the basal level at 5 min after administration of secretin is presumptive evidence of Z-E Syndrome. A response of less than 110 pg/ml makes the diagnosis extremely unlikely." (Page 22 of review)*

An article by McGuigan and Wolfe in 1980 reviewed the published literature to date[1]. The authors discussed several reports in which the secretin test was found to be less

accurate in diagnosing ZE than the studies in the NDA 18-290 submission. These authors pointed out the differences in secretin product (Boots versus GIH), dose, method of infusion, timing of serum sampling, and criteria for diagnosis in the studies. These differences were felt to be the source of inaccuracy of the test in the cited reports. The authors specifically state that:

"At the present time there is insufficient information in the literature to compare secretin provocation results using the several available forms of synthetic porcine secretin with the results using the purified naturally occurring porcine secretins." [2]

It is worth noting at this point that the synthetic porcine secretin is significantly different than the GIH/Kabi natural purified product. The biologic Ferring product contains — — impurities according to the sponsor. These impurities are not characterized. They may represent biologically active gut hormones that may contribute to the gastrin releasing effect seen in the secretin test (or less likely account for the majority of the effect). Gastrin RIA crossreactivity with these peptides cannot be ruled out. The cautionary note in the McGuigan and Wolfe article about the need for experience with the synthetic product is therefore quite relevant to the current NDA.

In conclusion, the issues that must be addressed in this NDA include:

- Proof of concept that porcine secretin is the primary active moiety in BPS
- Comparative pharmacodynamic properties between BPS and SPS in non gastrinoma and gastrinoma subjects
- Diagnostic comparability

The study size needed to statistically address the third issue would require years to accrue. Therefore, qualitative review of the data will be necessary. If the data were to suggest substantial differences between the BPS and SPS, further studies may be needed to characterize the dynamic and diagnostic range of SPS independent from the literature-based data available for the BPS.

2 Clinical studies

2.1 Description of clinical data sources:

1. Study 97-2 Open Label use of SPS for the:

- Diagnosis of gastrinoma
- Facilitation of pancreatic duct cannulation
- Diagnosis of pancreatic exocrine function

This protocol was amended at one center, ([redacted] to include BPS as well as SPS in a crossover design. Three subjects from this center were included in the pivotal "meta-analysis" or pooled analysis of subjects from both the amended 97-2 and 99-8.

2. 99-10 Pharmacokinetic study of SHS and SPS in healthy volunteers including gastrin response
3. 99-8 Pharmacodynamic and diagnostic comparison between SHS, SPS and Ferring BPS for the diagnosis of gastrinoma

2.2 Clinical Studies

2.2.1 Study 97-2

Title: Synthetic Porcine Secretin open label clinical use protocol

Objective: To obtain supplemental pharmacological efficacy and safety data in standard clinical use for the diagnostic indications approved for the extracted product.

Design:
Multicenter, open-label, non-comparative clinical use study of SPS as a diagnostic agent for chronic pancreatitis, pancreatic cancer, gastrinoma and to facilitate pancreatic duct cannulation during ERCP.

Protocol: Patients with suspected gastrinoma received a dose of 0.4 micrograms/kg SPS and had blood samples obtained at pre-dose and 1, 2, 5, 10 and 30 minutes post –dose for serum gastrin concentration.

Reviewer commentsxs:
The sponsor did not specify clinical inclusion criteria for suspected gastrinoma. Thus, careful review of the clinical presentation of each subject would be necessary as part of any attempt to interpret diagnostic efficacy from this study.
The Ferring secretin label states that the patient should have fasted for 12 hours. The sponsor did not state in protocol 97-2 whether subjects had fasted for 12 hours.

Efficacy endpoint:

Diagnosis of gastrinoma based on elevation of serum gastrin concentration from baseline.

Reviewer Comment:
The sponsor did not define diagnostic serum gastrin concentration parameters for the test. The approved Ferring secretin label states:

" Gastrinoma is strongly indicated in patients with elevated fasting serum gastrin concentrations in the 120-500 pg/ml range (determined by RIA using the antibody to

gastrin similar to that prepared by — and in patients who show an increase serum gastrin concentration of more than 110 pg/ml over basal level."

Statistical considerations:

No statistical plan was proposed for this uncontrolled study.

Reviewer's comment:

As the entire database of subjects with confirmed gastrinoma studied in a comparative crossover manner in this NDA includes 7 subjects (plus one cured patient with a normal BPS based SST) divided between study 97-2 and 99-8 the results will be review together after review of the protocol for 99-8.

2.2.2 Study 99-8

Title: A randomized, controlled, crossover study evaluating synthetic porcine for the diagnosis of gastrinoma

Objective: To obtain comparative pharmacologic and safety data from SPS, SHS and BPS as diagnostic agents in patients with a diagnosis of gastrinoma

Inclusion criteria:

1. Males or females of non-childbearing potential
2. Patients with a diagnosis of gastrinoma documented by a prior secretin stimulation test with BPS and by clinical and laboratory findings consistent with this diagnosis

Reasons for exclusion:

1. Active acute pancreatitis
2. Anticholinergic medication within one week of testing
3. Known sensitivity or adverse reaction to secretin
4. Pregnant or nursing female
5. Any medical condition, which in the judgement of the investigator would prevent the patient from safely undergoing testing

Randomization: The protocol stipulated that "Each patient will receive all three study drugs in random sequence. SPS, SHS and BPS will be dispensed in identical appearing syringes to ensure blinding to the patient."

Reviewer's Comment:

The sponsor did not indicate how the investigator was to be blinded. Investigator blinding is more critical for this trial than patient blinding. In the third interim report dated April 12, 2000 on the meta-analysis of studies 99-8 and amended 97-2 the sponsor states that the patients were randomly assigned by lot to one of three Latin square sequences of administration of the three drugs. This was to "balance any theoretic effects" (carryover). The small size of the study does not allow for this potential confounding factor to be assessed.
In the third interim report the blinding is described as follows:
"A research pharmacist not involved with the clinical aspects of the study, reconstituted study drug and dispensed doses in blinded syringes. ***The study personnel were informed of the sequence of administration for each patient after the patient completed the study.***"
It is unclear why the study personnel were informed of the identity of the drug at any time before the final analysis of data. The potential for bias is noted.

Administration of secretin:

The dose of secretin was 2CU/kg of BPS or 0.4micrograms/kg of SPS over 1 minute intravenously.

Study outline

Patients meeting all inclusion/exclusion criteria will receive an initial intravenous dose of 0.1 mL (0.2 μg sPS or sHS or 1 CU bPS).). If no allergic reaction is noted after one minute the full dose will be administered.

. Each patient will undergo blood draws for gastrin levels at baseline (prior to administration), 1, 2, 5, 10, 15, 20, and 30 minutes post secretin injection

At least 2 hours from the end of the procedure will elapse between treatment periods.

Patients whose test or test results are incomplete or technically inevaluable will be replaced and receive the same treatment sequence. All patients receiving study drug will be evaluated for safety.

Patients will fast for at least 12 hours prior to the scheduled tests and report to the study center on the morning of the test.

Reviewer's Comment:

The protocol calls for a two-hour washout period to elapse between each SST. During a telecon the sponsor stated that the pharmacokinetic effect of the drug is on the order of several minutes and that 2 hours is an adequate washout period. The division raised concerns over the time required for a gastrinoma to recover the capacity to respond maximally to repeat secretin injections over a short period of time. As noted previously, the small size of the study prevents any meaningful analysis of carryover effect. This is particularly problematic in view of the short period prespecified between stimulation tests.
A written response from the sponsor dated March 8, 2000 stated that the sponsor's consultants agreed with the agency that physiological recovery of the tumor is the relevant issue rather than the pharmacokinetic of the hormone. The consultants' letters are reproduced below and confirm the fact that there are no data available to make even a physiologically based suggestion as to the proper washout period for pharmacodynamic study purposes.

March 1, 2000

Seymour Fein, M.D.
ChiRhoClin, Inc
15500 Gallaudet Avenue
Silver Spring, MD 20905

RE Secretin Stimulation Test for ZE Syndrome

Dear Dr Fein,

This letter is to document my oral expression to you that I believe one day intervals are adequate to provide accurate and consistent results comparing administration of several forms of secretin in assessment of serum gastrin concentrations in response to intravenous secretin injection This test is used in evaluation of patients with potential Zollinger Ellison Syndrome My opinion is based on the extremely brief circulatory half-life and biological effects of secretin on serum gastrin levels I am not aware of any investigative data which support or reject direct or indirect effects extending beyond the first 60 to 30 minutes after secretin administration. In fact, principal gastrin release occurs in most patients with the Zollinger-Ellison Syndrome within two minutes of intravenous secretin injection I do not know of any data suggesting or confirming that differences in biological responses would be anticipated within a range of one day to several weeks. I do not anticipate that differing intervals between intravenous secretin injection would affect results or interpretation of results.

With my best wishes.

February 15, 2000

Seymour Fein, M.D.
15500 Callaudet Ave.
Silver Spring, MD 20901

Dear Dr. Fein.

You have asked me to give you an opinion regarding the appropriate timing interval for washing patients out from secretin testing. As I told you, there are no data that have looked at this in the past, although you might want to look at Harold Frucht's paper in Gastroenterology which might have had a couple of sequential tests. In my opinion, however, I think that since the biologic effect of secretin in testing for Zollinger-Ellison syndrome patients seems to last for no longer than about 20 or 30 minutes, I guess that doing tests on sequential days should be perfectly fine in terms of looking for an appropriate wash-out period. If you recall, when we first set up the study I was thinking of doing all three tests on the same day and if we want to go a 24 hour period between testing I think that would be totally appropriate. Unfortunately there are no firm data, but you will be able to at least get some patients who get tests on sequential days and others on larger intervals and you probably will be able to answer this question after your submission. Nevertheless, I really think it is a reasonable approach.

If I can be of any further assistance, please do not hesitate to contact me.

Yours sincerely,

The data submitted by the sponsor did not conform to the one day washout period for 2 out of 7 evaluable subjects in a combined analysis of studies 99-8 and 97-2.

Statistical Plan:
The statistical plan is limited and is reproduced below. The reader is referred to the statistician's review as well.

7.3 Statistical Plan and Methods

The study design is a three-way crossover Latin square in which the treatments are synthetic porcine secretin 0.4 µg /kg (Treatment A), synthetic human secretin 0.4 µg /kg (Treatment B), and biologically derived porcine secretin 2 CU/kg (Treatment C). The GLM procedure from Statistical Analysis System (SAS® Institute, Cary NC) will be used to test for treatment and carryover effect. Multiple comparisons and regression procedures will be utilized to compare Treatments A, B, and C Summary and descriptive statistics will be provided for the treatment effects.

Patients not completing all 3 treatments will be replaced.

7.4 Statistical Power of Study
It is anticipated that the response from baseline will be significant at $p <= .05$. No difference is expected among the treatment groups

Reviewer's Comment:

The statistical plan did not define any meaningful analysis. As noted earlier, the small size of the database precludes statistically meaningful analyses. Descriptive statistics may be of value in interpreting the data for qualitative consideration.

Conclusions on study design of 97-2 and 99-8:

The lack of rigorously defined protocols, entry criteria and statistical plans are of concern. These concerns further undermine the ability to draw conclusions from this small database. The two studies do, however, represent crossover studies of SPS and BPS that may shed some light on the biologic similarity of the two forms of secretin. The case reports on each subject will be critical to this review as the variability in the protocols and study population precludes reliance on group statistics. For this reason, no review of group statistics was done.

2.2.3 Combined results of studies 99-8 and amended 97-2

Due to the previously noted concerns over the washout period between the tests within the crossover model used in the database, lack of clear diagnostic and inclusion criteria and the small size of the database, it is critical to review each subject carefully and individually. The division requested early in the review cycle, clinical information on all subjects including duration of disease and primary source documents relating to the prior diagnosis. The following vignettes were constructed from the data supplied by the sponsor. The submission of the data did not follow any consistent pattern in terms of the type of source data that was provided.

Subject 99-8 subject #1 - age 28
Date and basis of original diagnosis: Not given.
Clinical presentation of gastrinoma: not given
Supportive laboratory data: Gastrin 759, PTH elevated at 28 "numerous scans" unspecified and no results, EGD- no results
Date and time of SPS based SST
Date and time of SHS based SST
Date and time of BPS based SST
No prior SST or definitive diagnostic criteria described in the submitted material

Subject 99-8 subject #2 - age 45
Date and basis of original diagnosis: [redacted] surgical pathology (SST done after surgical resection)
Clinical presentation of gastrinoma: not given
Supportive laboratory data: Resting Gastrin 601, elevated BAO, hypertrophic folds on EGD
Date and time of SPS based SST
Date and time of SHS based SST
Date and time of BPS based SST

Subject 99-8 subject #3 - age 47
Date and basis of diagnosis: "1980's" with MEN and surgical resection of gastrinoma previously.
Clinical presentation of gastrinoma: routine yearly follow-up with chronic recurrent abdominal pain 1999
Supportive laboratory data: One year prior to enrollment: EGD WNL, SST 1999, BAO 12.5 mEq/hr (WNL),
Date and time of SPS based SST

Date and time of SHS based SST
Date and time of BPS based SST
Note : serial SSTs done in less than 24 hours

Subject 99-8 subject #4 — age 72
Date and basis of diagnosis: 1998 biopsy of duodenum "neuroendocrine tumor", SST done 1998, EGD with duodenitis and esophagitis, "gastric analysis" results not given.
Clinical presentation of gastrinoma at time of protocol: not given
Date and time of SPS based SST
Date and time of SHS based SST /
Date and time of BPS based SST
Note: serial SSTs done in less than 24 hours

Subject 99-8 subject #7 — age 43
Date of dx and basis of diagnosis: "1980's" with MEN syndrome, elevated gastrin level and perforated DU; : biopsy proven duodenal gastrinoma 1999
Clinical presentation of gastrinoma at time of protocol: routine follow-up asymptomatic on Prilosec 20 mg bid
Date and time of SPS based SST
Date and time of SHS based SST /
Date and time of BPS based SST
NOTE: 3 SERIAL SST DONE WITHIN 4 HOURS

No information given on subjects #5 and 6 from study 99-8

Subjects from amended study 97-2

Subject 97-2 subject #001 — age 57
Date and basis of diagnosis: not given for pre-op evaluation (however surgical resection performed shortly after protocol)
Clinical presentation of gastrinoma at time of protocol: not given
Supportive laboratory data: following protocol, diagnosis confirmed at surgery
Date and time of SPS based SST
Date and time of SHS based SST NOT DONE
Date and time of BPS based SST —

Subject 97-2 subject #002 — age 55
Date and basis of diagnosis: (total gastrectomy for biopsy proven gastrinoma 1996)
Clinical presentation of gastrinoma at time of protocol: No documentation of status of gastrinoma other than SST done for protocol purposes
Supportive laboratory data:
Date and time of SPS based SST —
Date and time of SHS based SST NOT DONE
Date and time of BPS based SST —

NOTE: 1. protocol violation: 75 instead of indicated 80 CU of BPS used to avoid wasting BPS (each vial has 75 CU)
2. serial SSTs performed within less than 24 hours

Subject 97-2 subject #03 — age 77
Date and basis of diagnosis: several months prior to protocol, pancreaticoduodenectomy for metastatic gastrinoma per MD f/u note.
Clinical presentation of gastrinoma at time of protocol: No documentation of status of gastrinoma other than SST done for protocol purposes
Supportive laboratory data: none other than protocol based SST
Date and time of SPS based SST —
Date and time of SHS based SST NOT DONE
Date and time of BPS based SST —

NOTE: BPS derived samples not sent to investigator center lab. Results generated by apparent outside lab. —

In summary:

1. **A total of eight subjects were presented in the pooled analysis of studies 99-8 and amended study 97-2.**
2. **Subjects from study 99-8 (#5 and 6) are not identified. The clinical study report section on disposition of subjects simply states that 5 subjects were enrolled. This discrepancy should be clarified.**
3. **One subject received 6% less BPS than the protocol prescribed diagnostic dose. This deviation is noted but is unlikely to impact the results.**
4. **The sponsor did not include information on the type of assay used to measure the serum gastrin concentrations in the study. It appears that at least one subject had the two SSTs gastrin measurements done by different labs. It is not clear what potential effect this fact may have on the comparative results.**
5. **One of the eight subjects had a curative surgery before the study and had normal values for both BPS and SPS at the time of the protocol. This subject may be useful for pharmacodynamic comparability in some general sense but cannot be included in a rigorous analysis of active gastrinoma subjects.**

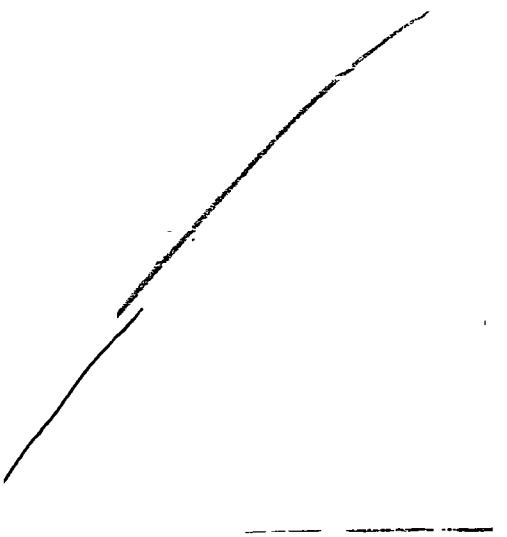
6. **Five out of the seven potentially evaluable subjects had 2 SSTs performed within less than 24 hours of one another** (3, 3, $23^{1/2}$, $22^{1/2}$, $22^{1/2}$ hours). One of these subjects had three SSTs performed within $4^{1/2}$ hours. The baseline gastrin level for the second and third SSTs were 1000pg/mL higher than the first SST suggesting that the subjects serum gastrin level was still reflective of the stimulation of the first SST when the baseline for the second test was measured. This is highly problematic when attempting to analyze the comparability of two products. The fact that all three tests were consistent and positive is important but does not mitigate the need for pharmacodynamic comparisons. This lack of consistency in washout period and absence of independent confirmation of the lack of carry-over effect associated with such short washout periods remains problematic and lessens this reviewer's confidence in considering this small database for assessment of diagnostic range. ***One may accept this database as adequate evidence only if the implicit hypothesis that the diagnostic ranges are the same for the SPS and the BPS has already been accepted.***

Results of individual secretin stimulation tests:

Table 2

POOLED SERUM GASTRIN CONCENTRATIONS (pg/mL)

Sub. #	Initials	Study	Drug	Baseline	1 min	2 min	5 min	10 min	15 min	20 min	30 min
1		97-2	sPS								
1		97-2	bPS								
2		97-2	sPS								
2		97-2	bPS								
3*		97-2	sPS								
3		97-2	bPS								
4(01)		99-8	sHS								
4(01)		99-8	sPS								
4(01)		99-8	bPS								
5(02)		99-8	bPS								
5(02)		99-8	sPS								
5(02)		99-8	sHS								
6(03)		99-8	bPS								
6(03)		99-8	sPS								
6(03)		99-8	sHS								
7(04)		99-8	sHS								
7(04)		99-8	sPS								
7(04)		99-8	bPS								
8(07)		99-8	sHS								
8(07)		99-8	sPS								
8(07)		99-8	bPS								



*Patient #3 had previously tested positive for gastrinoma with sPS. After curative resection of a gastrin secreting islet cell tumor tests with sPS and bPS were negative.

Table 3

DIAGNOSTIC OUTCOMES (CRC99-8 & 97-2)

Subject #	sPS	BPS	Tissue Dx
1	+	+	+
2	+	+	+
3*	-	-	-
4(01)	+	+	+
5(02)	+	+	+
6(03)	+	+	+
7(04)	+	+	+
8(07)	+	+	+

* Subject 3 had positive tests with sPS in 1999 but then had curative resection of a gastrin secreting duodenal islet cell tumor.

Tables 2 and 3 indicate that the two preparations had diagnostic concordance in the 7 cases presented in the database. Table 4 displays comparisons between the two study drugs for baseline gastrin levels. Qualitatively there does not appear to be any greater difference between the baseline gastrin levels of the BPS and SPS based SSTs in the subjects with "data quality issues" (#1,2,7,8) than the remaining subjects (#4,5,6) {using numeration of the sponsor-generated table 2 above}.

Table 4

Intra-individual variability of baseline and 5 minute stimulated results

Subject #	% difference between baseline gastrin (SPS/BPS x100)	Absolute difference between baseline gastrin levels (SPS-BPS)
#1	127%	61
#2	109%	28
#3	Excluded negative BPS SST	
#4	76%	-192
#5	151%	40
#6	51%	-71
#7	65%	-152
#8	99%	-20

There is no pattern in the Table above to suggest those subjects with shortest washout periods between SSTs (#7,8) {1 and 3 hours} had greater differences between baseline values than the remainder of the subjects with longer washouts of 22 hours or more. The

degree of variability in baseline gastrin concentrations is consistent with known biologic variability in serum gastrin concentrations and does not necessarily reflect study drug related variability.

Table 5 displays the pharmacodynamic responses of each subject at 5 minutes. This timepoint was chosen as the most frequent time by which a response is noted in the literature.[1] This also represents the time point most frequently associated with the peak levels of gastrin in the database.

Table 5

Subject #	% rise in serum gastrin concentration (pg/ml, from baseline to 5 minutes post SST)		Absolute rise in serum gastrin concentration (pg/ml, baseline to 5 minutes post SST)	
	SPS	BPS	SPS	BPS
1	117	137	335	307
2	35	64	120	199
3	excluded			
4	52	58	315	467
5	244	402	288	314
6	249	114	184	166
7	160	174	477	749
8	56	85	1750	2660

Reviewer's Comment:
There is no pattern that clearly differentiates the results from subjects #7 and 8 (those with 1 and 3 hours washout) from the other subjects. There is a suggestion that the differences in the absolute rise in gastrin concentration are greater for the subjects with the shortest washout (#7,8) compared to the other subjects. If these subjects were excluded from any formal statistical analysis the variability in the results generated from the 2 products would decrease suggesting a better correlation between the two tests. Thus it is in fact more conservative to include the data from these two subjects in any analysis. Of note is that only one subject had a gastrin concnetration response that was anywhere near the diagnostic cutoff. ***This subject did have a large difference between the two tests raising the possibility that in borderline cases there may be a loss of accuracy. The sample size of the study is too small to even qualitatively examine this issue.***
In six out of the seven cases BPS was associated with a greater % rise in serum gastrin concentrations. In five out of the seven cases BPS was associated with a greater absolute rise in gastrin concentrations than SPS. This trend towards a larger pharmacodynamic effect in the BPS dosed SSTs to diagnose ***gastrinoma*** *is consistent with the trend that was seen in the pharmacodynamic effect that was seen in the SST to* ***diagnose pancreatic insufficiency*** *study in NDA 21,136.*

The questions raised by a detailed review of the database highlight the difficulty in drawing conclusions from such a small study.
It is important to highlight (as the advisory committee did prior to the approval of the Ferring BPS product 20 years ago) that great variability is to be expected in any bioassay for a condition with great heterogeneity such as pancreatic insufficiency or gastrinoma. Therefore diagnostic accuracy data would have been more meaningful that pharmacodynamic data for clinical practice. Unfortunately, the rarity of gastrinoma as an illness limits the ability to collect the volume of cases to assess the diagnostic accuracy or "calibrate the diagnostic range" for the proposed SPS independent of the historical data available for the Ferring SPS product.

Conclusions from analysis of the pooled data from studies 97-2 and 99-8:

1. ***The very limited data presented suggest that the sensitivity of the proposed SPS product is similar to the approved Ferring BPS product. Specificity cannot be assessed independent of extrapolation of BPS based literature because there are no data to assess this diagnostic parameter***
2. ***The pharmacodynamic similarities are less consistent than the diagnostic concordance, as would be expected in such a bioassay.***
3. ***The tendency towards larger responses to BPS suggest that there may be a need to independently "calibrate" the diagnostic range for SPS to obtain similar diagnostic accuracy for this product compared to BPS.***

2.2.4 Study 97-2 (unamended)

Subjects in the unamended protocol 97-2 underwent open label use of SPS based SSTs. Review of the data presented by the sponsor reveals that little clinical information was included. This fact prevents any qualitative assessment of the diagnostic accuracy of the SPS based SST test in those subjects that had negative tests. Clinical data to independently confirm the diagnosis of gastrinoma in the positive subjects with a positive SST was lacking in majority of cases. Thus, this open label usage study cannot be used to assess positive or negative predictive value of the SPS based SST.
The data are partially summarized below.

97-2 negative SST subjects from 2/3/00 submission
12 subjects:
no data on clinical indication

97-2 positive SST subjects from 2/3/00
4 subjects: **No Clinical data**
3 subjects: **Clinical data provided to corroborate the diagnosis of gastrinoma independent of current protocol**

Reviewer's Comment:
This open label portion of study 97-2 did not provide inclusion criteria or mandate adequate clinical data collection to provide quantitative or even qualitative information on the value of the SST using the proposed SPS. It is concluded that this study does not allow for any bridging between the approved Ferring biologic product and the proposed SPS.

2.2.5 Study 99-10

"A single center study evaluating the pharmacokinetic profile of a single intravenous dose of synthetic porcine secretin and synthetic human secretin in normal subjects."

This title suggests that the primary goal of this study was to assess pharmacokinetics. A secondary objective was the evaluation of the effects of SPS and SHS on serum gastrin levels in normal subjects. The sponsor did not indicate which assay was used to measure serum gastrin levels in this study.
The washout period between SSTs was set at 1 week.
Each subject received 0.4 micrograms/kg SPS intravenously over 1 minute.

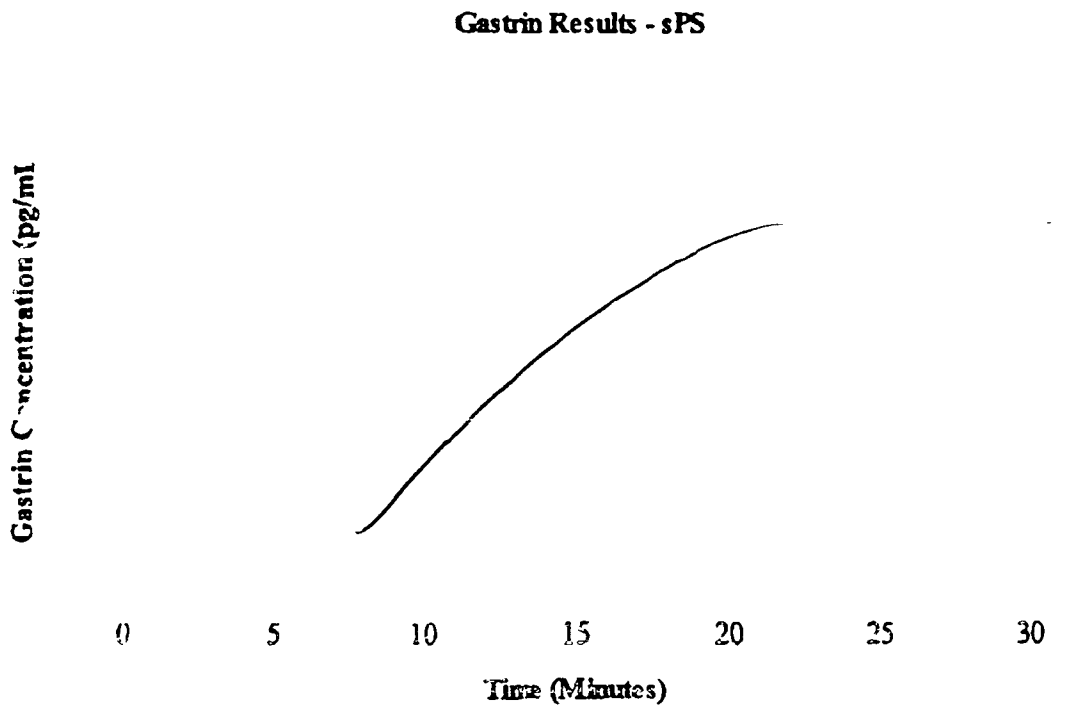
Results:

Table 6

GASTRIN CONCENTRATION (pg/mL) FOR SPS

Subject No.	0 Minutes	2 minutes	4 Minutes	10 minutes	15 minutes	30 Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						

Graph 1



Reviewer's comment:

1. The timing intervals for post-dose blood collection were different in this study than in the other studies in this submission and in the Ferring product label. It is unclear why 4 rather than 5 minutes was chosen. However, this difference is not expected to affect the value of the data collected.
2. The data are consistent with the medical literature, which suggests that normal subjects do have a small rise in serum gastrin concentration in response to SST, using the Ferring product. This rise is early (within the first 2-4 minutes) and much more modest than that seen in gastrinoma patients. Thus, this small study is reasonably convincing that in healthy subjects SPS produces a response similar to that seen with the approved and historically studied biologic porcine secretin. As noted earlier in this review, similar results can be extrapolated for those conditions that are associated with a physiologic increase in fasting unstimulated serum gastrin levels such as achlorhydria and G-cell hyperplasia.
Extrapolation to these groups without any supportive data requires an assumption that the impurities present in the biologically derived secretin will not significantly affect the gastrin response in these conditions. This reviewer is willing to accept this assumption.

The lack of an exaggerated or paradoxical response to the SST using the Ferring product in these conditions strongly suggests that a purer secretin product would continue to show this lack of stimulatory effect on serum gastrin levels in these other conditions. Likewise, in patients with a clinical presentation that suggests gastrinoma but have normal gastrin levels (aggressive duodenal ulcer disease and or diarrhea) there is no reason to suspect an abnormal response to a synthetic more pure form of secretin compared to the biologic product.

Conclusions: Study 99-10 supports the conclusion that SPS produces a modest rise in fasting serum gastrin concentration in healthy volunteers. This is consistent with the medical literature related to BPS. This modest rise is unlikely to impact on the diagnostic value of SPS to any greater extent than it has impacted on the diagnostic value of Ferring BPS.

2.2.5 Integrated Summary of Diagnostic Efficacy

As noted early in this review, proof for three hypotheses was need from this NDA. These hypotheses are related and progressive. The first requires less rigorous data. The second requires more extensive data to prove and the third would require a larger database yet.

1. Proof of concept that porcine secretin is the primary or only active moiety in BPS for use in the SST for the diagnosis of gastrinoma.
2. BPS and SPS produce comparable pharmacodynamic results in serum gastrin concentration in gastrinoma and non-gastrinoma subjects
3. Diagnostic accuracy for the two products are comparable

Despite the small database, the rise in serum gastrin concentration associated with the biologic and less pure secretin was similar enough to the synthetic product to indicate that the secretin peptide is in fact the primary active moiety responsible for the exaggerated rise in gastrin concentration associated with the SST.

The pharmacodynamic results were too limited to define the pharmacodynamic similarity or difference with any meaningful degree of certainty. However, the data were similar enough to indicate that the tests would not result in such differences that the newer agent could not give "meaningful" results in clinical practice. The data do indicate that the SPS has diagnostic value.

The degree of value in practice however depends on defining a diagnostic range that can be interpreted by the practicing physician. Even a diagnostic test with much less accuracy than the apparent accuracy of the SPS based can be useful in practice as long as the interpreting physician knows how to interpret the results. Knowledge of the limitations of the test at hand allows the clinician to decide on when to use other diagnostic modalities. If a labeled diagnostic range for the SPS based SST is accepted as the gold standard for the diagnosis of gastrinoma then other confirmatory tests would rarely be considered necessary. Gastric analysis and calcium stimulation tests are less frequently relied upon due to the acknowledged high degree of sensitivity and specificity associated with the diagnostic cutoff of 110 pg/ml for the BPS based SST. The small database does not allow for reasonable assurance that the diagnostic cutoff is the same for SPS and the BPS based SSTs. In fact there is a suggestion from the results reported in the current NDA and NDA 21,136 that the pharmacodynamic activity of the two products may be slightly different for both the gastrinoma and pancreatic insufficiency tests. Thus, the diagnostic interpretation of results that are close to the currently accepted diagnostic cutoff for BPS may not be as accurate with the SPS based SST.
In summary, although, diagnostic efficacy can be accepted based on the this NDA, the optimal diagnostic range is less well characterized than for the BPS product.

3. Safety review of NDA 21,209

Before discussing the safety database of the current submission several excerpts from the safety review of NDA 21,136 are provided.

3.1 Studies 97-1, 98-1 and 98-2

Excerpt from review of NDA 21,136

Of the 27 patients in the controlled database one experienced flushing with both the 0.2 and 0.4 microgram/kg dose as well as with the BPS product. This patient did not have such a reaction to the lowest dose of SPS 0.02microgram/kg. The reaction was therefore dose related and likely to be drug related. Another patient experienced a headache that was self limited and lasted five hours. There was one patient in the synthetic porcine secretin database that experienced flushing following secretin administration.

Additional relevant safety data are available from [redacted] *Study 98-3B is a completed double blind placebo controlled study of the safety and efficacy of secretin for the treatment of autism and related pervasive developmental disorders. This single dose study included placebo, low (0.2 micrograms/kg) and high (0.4micrograms/kg) dose groups of 10 subjects each.*
Temporally related vasodilatation or flushing occurred in 2/10 subjects receiving the low dose and 1/10 patients receiving the high dose SPS. 0/10 subjects in the placebo group reported temporally related vasodilatory symptoms on the day of treatment.
In a second phase of this study all thirty subjects received the high dose of SPS; 2/30 subjects in this group experienced temporally related vasodilatation of the hands, face, neck and trunk. Although the proposed synthetic porcine secretin was not used in this study, one cannot rule out the possibility that this event may be physiologic and occur in association with porcine secretin.

The database of the large placebo controlled pancreatitis prevention study (97-3) within the NDA 21,136 submission was examined for hypotensive effects that may be associated with a clinically relevant vasodilatory effect. The results appear in table 21.

Table 21

	Secretin	***Placebo***
Greater than 9 point drop in systolic BP	*48/89 (54%)*	*43/86 (50%)*
Greater than 19 point drop in diastolic BP	*34/89 (38%)*	*30/86 (35%)*
Greater than 9 point drop in diastolic BP	*43/89 (48%)*	*31/86 (36%)*
Greater than 19 point drop in diastolic BP	*20/89 (22%)*	*14/86 (16%)*

There are missing blood pressure data on 36/125 (29%) of the secretin treated patients and 39/125 (31%) of the placebo treated patients. This is surprising since this is a clinically mandated measurement on any patient undergoing ERCP. This missing data and the lack of control for sedation and analgesia during ERCP limit the conclusions that may be drawn from this data The trend towards more hypotension in the SPS group is of note but no conclusions can be made from this data. It is clear however that the underlying treatment of all subjects with sedatives and analgesics accounts for much of the hypotensive effect seen in the study.

Safety Summary

1. *Synthetic human secretin may cause mild vasodilatation in up to 20 % of subjects receiving a single 0.2-microgram/kg injection. This effect was seen in association with synthetic porcine secretin as well.*
2. *A modest hypotensive effect of secretin may exist. This is unlikely to be of clinical significance unless superimposed upon other hypotensive agents in a patient with marginal circulatory reserve.*
3. *Secretin usage may be associated with clinically moderate to severe adverse events in the setting of ERCP. Although the sponsor is not proposing the use of secretin in the setting of ERCP, any future study of secretin in this setting will need to address concerns raised based on review of the database thus far collected.*
4. *No safety information is available regarding repeated dose exposure or exposure above 0.4 microgram/kg.*
5. *No data on drug-drug interaction is available. Currently available knowledge would not suggest any such interaction, other than possibly transient enhancement of the hypotensive effects of concomitant hypotensive therapy.*

End of excerpt

3.2 Safety review of NDA 21,209

In view of the suggestion of a potential hypotensive effect and vasodilatory effect in the database of NDA 21,136, IND — and the circulatory effects in preclinical studies listed in table one of the current NDA, adverse events potentially related to the circulatory system are worthy of careful scrutiny.
The current database is quite small. There are no placebo-controlled data, Nonetheless, the SST for the diagnosis of gastrinoma involves little intervention beyond blood drawing. Therefore, temporally related events after secretin injection may be potentially related to the administration of the drug. In the final amendment to the submission dated APRIL 14TH, 2000 the safety evaluation section of the clinical study report is four lines long and states that no adverse events have been reported. The Tables related to safety were reviewed. The data listing for adverse events were not consistent with the statement in the narrative safety report in section 12.0 of the study report in the submission of April

14, 2000. This table in reproduced in Table 7. Of note is that only 5 subjects were enrolled in this study. 2/5 subjects had symptoms described as moderate and probably associated with the drug.

Table 7

DATA LISTING 8
ADVERSE EVENTS

Sub. #	Period	TRT	Event	Onset Time	End Time	Con-tinuing	Severity	Relationship to Study Drug	Action	Outcome
1	1	sHS	Tingling in both legs	12:25	12:27	No	Mild	Probable	None	Resolved
1	2	sPS	Burning in stomach	11:13	11:19	No	Moderate	Probable	None	Resolved
1	2	sPS	Sweating hands	11:13	11:19	No	Moderate	Probable	None	Resolved
1	2	sPS	Sweating feet	11:13	11:19	No	Moderate	Probable	None	Resolved
1	2	sPS	Burning in stomach	11:46	12:00	No	Moderate	Probable	None	Resolved
3	1	bPS	Hot burning sensation in abdomen	11:26	11:31	No	Moderate	Probable	None	Resolved
3	2	sHS	Upset stomach	10:57	11:02	No	Moderate	Probable	None	Resolved
3	2	sHS	Burning in stomach	10:57	11:02	No	Moderate	Probable	None	Resolved
3	3	sPS	Burning in stomach	13:05	13:08	No	Mild	Probable	None	Resolved

The events in table 7 are similar to those noted in the human secretin database from IND → and 21,136.

A review of the case report forms from the five enrolled subjects in study 99-8 was performed. These data are displayed in table 8. One out of four subjects exposed to SPS had a systolic blood pressure drop of 10 (101to 91) and two subjects exposed to BPS had similar magnitude drops.

Table 8

Subject #	BPS		SPS	
	pre-dose BP	post dose BP	Pre-dose BP	Post-dose BP
99-8 #1	133/98	123/67	147/78	152/94
99-8 #2	133/66	121/79	142/80	144/90
99-8 #3	109/82	120/84	101/54	91/52
99-8 #4	140/88	138/97	144/88	138/88
99-8 #7	136/88	132/104	Not done	138/95

In the study report for study ***99-10***, adverse events compatible with vasodilatation were seen. These are displayed in table 9.

Table 9

TABLE 10
ADVERSE EVENTS

Sub #	Period	TRT	Event	Onset Time	End Time	Continuing	Severity	Relationship to Study Drug	Action	Outcom
1	1	A	Headache	11 15	12 30	---	Mild	Possible	None	Resolved
3	1	A	Nausea	11:00	12 00	---	Mild	Possible	None	Resolved
3	1	A	Numbness left hand and fingers	11:00	12:00	---	Mild	Unlikely	None	Resolved
3	1	A	Tingling left hand and fingers	11:00	12:00	---	Mild	Unlikely	None	Resolved
9	1	A	Lightheadedness	11.10	11:20	---	Mild	Unlikely	Placed in recumbent position, cool cloth to forehead	Resolved
9	1	A	Pallor	11 10	11 20	---	Mild	Unlikely	Placed in recumbent position, cool cloth to forehead	Resolved
9	1	A	Diaphoresis	11 10	11.20	---	Mild	Unlikely	Placed in recumbent position, cool cloth to forehead	Resolved
9	1	A	Hypotension	11 10	11.20	---	Mild	Unlikely	Placed in recumbent position, cool cloth to forehead	Resolved
3	1	A	Lightheaded	11.05	11 19	---	Moderate	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Diaphoresis	11:05	11 19	---	Moderate	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Thready Pulse	11:05	11 24	---	Moderate	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Lightheaded	11 19	11.24	---	Mild	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Diaphoresis	11.19	11:24	---	Mild	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Hypotensive	11 05	11.14	---	Moderate	Unlikely	Trendelenberg, cool cloth applied	Resolved
13	1	A	Hypotensive	11:14	11 19	---	Mild	Unlikely	Trendelenberg, cool cloth applied	Resolved

1- TRT A = sPS

2- Subject number thirteen was felt by the principle investigator to have had a vasovagal reaction to the IV itself which infiltrated and only gave a fractional dose of sPS subcutaneously

In the data listing for this study, subject #3 had a drop in blood pressure associated with both study periods. Subject 9 had no significant drop in blood pressure in the Table listing for blood pressure but in the adverse event table had "hypotension, pallor, diaphoresis and lightheadedness listed for the same study period. In the case report form submitted with the final study report for study 99-10 that was included in the NDA 21,256 the pre-dose vital signs were 135/79 pulse 89. Four minutes post dose the BP was 81/42 and the pulse was 57. The BP and pulse normalize within 10 minutes. This may simply have been a vasovagal response to phlebotomy. The second period blood pressure however also fell albeit less significantly and without associated bradycardia (148 to 136 systolic). The other evidence of hypotensive events associated with the drug indicates that drug effect cannot be excluded entirely as related to this event.
Subject #13 also had a hypotensive and bradycardic response to a partial dose delivery. The subject's IV infiltrated before the entire dose was delivered. The monitor noted that

"partial dose given". Baseline BP and pulse were 143/82 –64. Four minutes after the infusion the values were 89/39- 41. Within 15 minutes the vital signs had corrected. All three subjects with adverse events had associated drops in blood pressure. Two of the three may have been unrelated to the study drug (vasovagal episodes). The third subject however had no other likely explanation

The data table listing for the vital signs for study 99-10 is displayed in table 10.

Table 10

DATA LISTING 5A
PRE/POST-DOSE VITAL SIGNS RECORD

Sub #	Period	TRT	Time	Blood Pressure mm/Hg	BP Systolic mm/Hg	BP Diastolic mm/Hg	Pulse /minute	Respirations	Temperature °C
1	1	A	Pre-dose	124/85	124	85	75	17	ND
1	1	A	Post-dose	124/82	124	82	78	14	36.6
1	2	B	Pre-dose	129/85	129	85	72	16	ND
1	2	B	Post-dose	126/76	126	76	71	16	36.7
2	1	A	Pre-dose	138/77	138	77	80	12	ND
2	1	A	Post-dose	118/79	118	79	63	16	36.3
2	2	B	Pre-dose	132/83	132	83	75	16	ND
2	2	B	Post-dose	120/78	120	78	65	16	36.9
3	1	A	Pre-dose	100/72	100	72	83	12	ND
3	1	A	Post-dose	90/58	90	58	71	14	36.3
3	2	B	Pre-dose	99/64	99	64	61	16	ND
3	2	B	Post-dose	91/56	91	56	69	16	36.8
4	1	A	Pre-dose	103/65	103	65	69	12	ND
4	1	A	Post-dose	106/70	106	70	69	16	37.1
4	2	B	Pre-dose	104/71	104	71	67	12	ND
4	2	B	Post-dose	114/75	114	75	77	14	36.8
5	1	A	Pre-dose	108/63	108	63	62	12	ND
5	1	A	Post-dose	122/76	122	76	63	12	36.4
5	2	B	Pre-dose	120/73	120	73	52	16	ND
5	2	B	Post-dose	117/69	117	69	58	16	36.7
6	1	A	Pre-dose	119/75	119	75	59	14	ND
6	1	A	Post-dose	114/64	114	64	55	16	36.6
6	2	B	Pre-dose	116/72	116	72	61	16	ND
6	2	B	Post-dose	115/68	115	68	64	16	36.4
7	1	A	Pre-dose	100/63	100	63	71	18	ND
7	1	A	Post-dose	99/57	99	57	70	16	37.1
7	2	B	Pre-dose	107/70	107	70	78	14	ND
7	2	B	Post-dose	89/57	89	57	60	16	36.8
8	1	A	Pre-dose	144/93	144	93	80	16	ND
8	1	A	Post-dose	124/88	124	88	79	16	36.6
8	2	B	Pre-dose	137/86	137	86	79	18	ND
8	2	B	Post-dose	126/79	126	79	82	14	36.8
9	1	A	Pre-dose	135/79	135	79	89	ND	ND
9	1	A	Post-dose	128/76	128	76	80	16	36.7
9	2	B	Pre-dose	148/80	148	80	106	20	ND
9	2	B	Post-dose	120/74	120	74	77	14	36.4

Table 10 (continued)

DATA LISTING 5A (continued)
PRE/POST-DOSE VITAL SIGNS RECORD

Sub #	Period	TRT	Time	Blood Pressure mm/Hg	BP Systolic mm/Hg	BP Diastolic mm/Hg	Pulse /minute	Respirations	Temperature °C
10	1	A	Pre-dose	122/56	122	56	79	16	ND
10	1	A	Post-dose	117/73	117	73	78	16	34.8
10	2	B	Pre-dose	107/70	107	70	74	16	ND
10	2	B	Post-dose	103/65	103	65	81	17	36.5
11	1	A	Pre-dose	125/86	125	86	84	20	ND
11	1	A	Post-dose	121/73	121	73	76	18	37.0
11	2	B	Pre-dose	119/76	119	76	69	16	ND
11	2	B	Post-dose	110/77	110	77	67	16	36.8
12	1	A	Pre-dose	148/94	148	94	91	ND	ND
12	1	A	Post-dose	124/85	124	85	71	16	37.1
12	2	B	Pre-dose	143/87	143	87	79	14	ND
12	2	B	Post-dose	121/83	121	83	69	16	37.0
13	1	A	Pre-dose	143/82	143	82	64	20	ND
13	1	A	Post-dose	ND	ND	ND	ND	ND	ND

(SPS was treatment A)
(SHS was treatment B)

In addition to the two possible vasovagal episodes three subjects (2,8,12) had systolic drops of 20 points or greater associated with dosing and an additional two subjects (3, 7) had drops in systolic blood pressure of at least ten associated with dosing. Thus seven out of twelve subjects (58%) had potentially clinically relevant drops in blood pressure associated with this study. In most of these cases there was some blood pressure drop associated with both the SHS and the BPS.

In summary:

- Significant systolic blood pressure drops are associated with the use of SPS, SHS and BPS in the database from both NDA 21,136 and 21,209 at single doses of 0.2 and 0.4 micrograms/kg. The higher dose of 0.4 micrograms/kg in the current NDA appears to be associated with a more significant hypotensive effect. These findings in a small database are difficult to assess. The symptomatic adverse events and the blood pressure changes are consistent with an effect on the circulatory system that has been documented in preclinical studies in the medical literature. This information should be included in the labeling

4. Integrated summary of benefits and risk

The benefits of a safe and accurate diagnostic test for the diagnosis of gastrinoma are clear and well articulated in previous NDAs for secretin as well as the medical literature. The medical literature is consistent in noting the high diagnostic accuracy of the test. There has been some difference of opinion regarding the optimal diagnostic cutoff. Most authors appear to concur with the label of the Ferring BPS, which indicates that:

" Gastrinoma is strongly indicated in patients with elevated fasting serum gastrin concentration in the range of 120-500 pg/ml range (determined by RIA using an antibody to gastrin similar to that prepared by — , and in patients who show an increase in serum gastrin concentration of more than 110 pg/ml over the base level."

Some authors in the past have suggested a cutoff of 200 pg/ml to avoid false positives. Interestingly, the concern over the proper cutoff was introduced based on cases of false positives reported in the literature. At least in some cases, the cause was found to be impurities in the secretin (Boot's) used that cross-reacted with gastrin in the immunoassay. Similarly in the current situation, the value of the SPS based SST has been confirmed by this small database supporting the large data base using the biologic product. The only outstanding issue is the optimal diagnostic cutoff. This can only be established with more extensive experience using the proposed SPS product. Until this issue is better clarified, the proposed SPS still remains an important tool in the evaluation of patients with symptoms suggestive of gastrinoma and an elevated fasting serum gastrin level as well as possibly monitoring for recurrence of disease.
Significant risks have not been identified with past usage of the SST. The current database does contain hypotensive events that may be related to the use of the SPS at the dose of 0.4 microgram/kg given intravenously over 60 seconds. Symptomatic hypotension and flushing which may be interpreted as secondary to vasodilatation also occurred in the database of other secretin NDAs. Effects on blood flow have also been noted in the preclinical literature. The sum total of the data reviewed does suggest that in some subjects significant symptoms and blood pressure changes do occur with this product. The high percentage of subjects (58%) that had meaningful drops in systolic blood pressure in this small database is of concern. Future studies of the diagnostic range of the SPS based SST should also include better characterization of the adverse event profile. Given the importance of this tool in the proper clinical setting; the risks demonstrated in the current database and the related NDAs and medical literature on biologic secretin products are outweighed by the benefits. Proper labeling and avoidance of improper usage of SPS should minimize the risks.

5 Recommendations for Regulatory Action:

1. **The proposed SPS product is approvable for the use as a diagnostic in the SST for the diagnosis of gastrinoma.**
2. **The label should —**

— should be stressed in the label with
Such data should include further comparative

data with the BPS product or independent data on the diagnostic range of the SST using the SPS.

3. **The label should reflect the potential for circulatory effects such as flushing and potentially clinically meaningful hypotension.**
4. **Further characterization of the adverse event profile of the proposed product should be obtained through further study.**
5. **The sponsor should also be requested to submit the following information before approval:**

a. **Identification and all case report forms and primary source documents on subjects #5 and 6**
b. **Identification of the assays for serum gastrin used in the database including the apparent outside laboratory associated with subject — (#3 from study 97-2).**

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Lawrence Goldkind M.D.

Concur. June 16, 2000

cc:
NDA 21-209
HFD-180
HFD-180/LTalarico 6-21-00
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/LGoldkind
HFD-181/PM
HFD-180/JChoudary
HFD-180/LZhou
f/t 6/14/00 jgw
N/21209006.0LG

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References:

1. McGuigan JE, Wolfe MM, Secretin injection test in the diagnosis of gastrinoma. Gastroenterology 1980, 79: 1324-31

MAR 17 2000

Division of Gastrointestinal and Coagulation Drug Products
Medical Officer's Review

NDA # 21-136

Submission Date: May 14th, 1999
Sponsor: ChiRhoClin

Generic name: Synthetic porcine secretin
Proposed trade name: ~~~~~

Structure: 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

Pharmacologic category: Polypeptide secretagogue

Proposed indications: 1. "For diagnostic use in pancreatic exocrine
3. "Diagnosis of gastrinoma"
4. "Facilitation of — during ERCP"

Indications filed: 1. "For diagnostic use in pancreatic exocrine dysfunction"

Indications not filed: 1. Diagnosis of Gastrinoma
2. Facilitation of — during ERCP

Dosage forms and route of administration: 0.2 μg/kg by intravenous (i.v.) injection over 1 minute for use in indications #1 and 2. And 0.4 μg/kg for use in indication #3.

Related drugs: Biologically derived porcine secretin (Ferring Labs). See section 6.2
The Ferring product is derived from porcine duodenal tissue and contains peptide impurities. According to the sponsor, the Ferring product has ~~~~~ impurities by weight compared to the proposed synthetic product.

Material reviewed:
1. NDA 21,136 submitted May 14, 1999
2. Amendment dated October 7, 1999
3. Amendment dated November 9, 1999
4. Amendment dated December 30, 1999
5. Amendment dated January 28, 2000

Related reviews: NDA 18-290 is the biologic secretin product initially submitted by Kabi and approved in 1981.The rights and production was subsequently transferred to Ferring. Ferring has informed the FDA that it has ceased production of this product as of June 1999. The current NDA 21-136 reviewer surveyed the review of NDA 18-290. The sections of note included:

1. Summary basis for approval dated May 29, 1981
2. Supplementary medical officer review: February 24, 1981 by Dr. T.Q. Harvey III
3. Medical officer's review dated June12, 1979 by Dr. Alan Schulman

Table of Contents

1. Materials reviewed: NDA 21-136 volumes 1-19
   Advisory committee meeting minutes 4/24/1978, 12/12/78, 6/1/79
   Medical officer's reviews 1979 through 1981
2. Chemistry/Manufacturing/ Controls : Refer to Chemistry review
3. Animal Pharmacology/Toxicology: Refer to Pharmacology/Toxicology review

4. Clinical Background

In 1902 Bayliss and Starling first showed that an extract from the gastrointestinal mucosa of pigs could stimulate pancreatic secretion in dogs. This was one of the earliest experiments documenting the generic concept of "hormonal" action. In 1962 purification of this porcine intestinal mucosal extract led to the sequencing of the 27 amino acid hormone, secretin. The carboxy-terminal is amidated. There is significant structural homology with other digestive hormones including vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP) growth hormone releasing factor and glucagon. This homology is preserved across species including human, bovine, porcine and canine. There is a 2 amino acid difference between the human and bovine sequences of secretin at amino acid position 15 and 16. Aspartamine and serine in the porcine molecule at these positions is replaced with glutamine and glycine in the human molecule.

The homology among multiple digestive hormones has made it difficult to precisely pinpoint the sites of secretin synthesis as well as secretin receptor distribution within the body. There are conflicting data regarding the presence of secretin activity in the central nervous system. RNA blot hybridization using tissue from the rat has indicated that the small intestine is the major site of secretin gene expression in this species. Secretin levels were highest in the ileum. Secretin RNA was below the level of detection in the stomach, cerebral cortex brainstem, hypothalamus, pituitary, and adult pancreas. Other studies using oligonucleotide primers for rat secretin, amplification of first strand cDNA suggested that secretin may be present at low levels in cerebral cortex, brainstem and hypothalamus. Other amplification studies in animals have suggested the presence of secretin in brain, kidney, heart and testis. These extremely sensitive methods of localization however, may be overly sensitive and produce artifactual results. The presence and potential role of secretin in these extraintestinal sites require further study and clarification.

Biological role of secretin:

Luminal stimulants to secretin release include gastric acid, bile salts, peptides, and long chain fatty acids. Cholinergic and adrenergic stimuli do not influence the luminal effects on secretin release. Starch does not appear to be a trigger for secretin release.

Table 1 displays the known effects of secretin. Not all are felt to be clinically relevant.

Table 1

	Secretin
Water-electrolyte secretion	
Stomach acid	*−
Pancreas	*+
Liver	+
Brunner's glands	+
Enzyme secretion	
Stomach	+
Pancreas	±
Intestine	+
Endocrine secretion	
Gastrin	*−
Insulin	+
Glucagon	±
Somatostatin	+
Smooth muscle	
Lower esophageal sphincter	−
Stomach	−
Intestine	−
Colon	−
Gallbladder	+
Sphincter of Oddi	−
Growth	
Gastric mucosa	−
Pancreas	±
Metabolic	
Lipolysis	+
Glycogenesis	
Cardiovascular system	
Heart rate	+
Stroke volume	+
Blood flow	
Superior mesenteric artery	+
Hepatic artery	−
Pancreatic artery	+
Small intestinal artery	+
Gastric mucosal artery	−
Femoral mucosal artery	+

*, Physiological action; +, stimulation; −, inhibition; ±, inconclusive; 0, no response.

Pharmacological uses for secretin have been investigated for over three decades since purified secretin became available. The Karolinska Instituet in Stockholm produced the most highly purified form in the 1970s. Manufacture of the product was transferred to Kabi Diagnostica in 1977. In 1981 the United States FDA approved Secretin-Kabi. It is derived from porcine tissue extract. It is indicated for the:

1. diagnosis of pancreatic exocrine function
2. as an adjunct in obtaining desquamated pancreatic cells for cytopathologic examination
3. diagnosis of gastrinoma (Zollinger-Ellison syndrome/ZE)

Ferring assumed production and marketing in 1989. As mentioned above, as of June 1999 Ferring has ceased production of their biologic secretin product.

4.2 Important information from related INDs and NDAs

The FDA approval of the marketing of Secretin-Kabi was based on published medical literature. The sponsor submitted no original experimental data.

The basis for approval for each indication is reviewed next.

Secretin in the diagnosis of pancreatic exocrine function:

Dr. Thomas Garvey III made several points in his supplementary review in 1981 related to the limitations of the secretin test for the diagnosis of pancreatic exocrine function.

"The secretin test for pancreatic disease has always occupied an ill-defined position in the hierarchy of diagnostic investigations for pancreatic disease. My assessment of the reasons for this on the basis of both personal experience and current review are:

1. *Duodenal drainage is not an easy technique. It usually requires fluoroscopic monitoring of the placement of the duodenal lumen of the double–lumen tube, and this step alone can take as long as two hours in inexperienced hands. Needless to say, patients do not like the tube and rarely appreciate the possible benefit that might accrue to them from successful execution of the test.*

2. *As pointed out by those two giants of gastroenterology, David Dreiling of Mt. Sinai Hospital in New York City and Morton Grossman of the Wadsworth Veterans Administration Hospital of Los Angeles, California, a relatively large number of patients shown conclusively to have no pancreatic disease must be investigated in each center in order to establish appropriate normal ranges for the volume and ion concentrations in pancreatic juice for that center.*

3. *Many investigators have sworn up and down that it is possible to distinguish pancreatic carcinoma from chronic pancreatitis using the secretin test. It is possible that in the hands of certain investigators this distinction can be made. This has, however, not been the usual experience.*

4. *Several new diagnostic techniques have become available in the last decade. Among them, CT-scanning, abdominal ultra-sound, percutaneous pancreatic biopsy, and endoscopic pancreatic cholangiopancreatography are all relatively benign, quite sensitive and somewhat easier to perform that the secretin test. Further, diagnostic arteriography has been considerable refined and is another valuable technique which has increased in usefulness for diagnosis of pancreatic malignancy in the last twenty years."*[1]

These points remain valid nearly twenty years later. Despite approval and availability of the secretin test, it is not a first line diagnostic test for pancreatic disease. Whether the indication for evaluation is pancreatitis, steatorrhea or abdominal pain, CT scan has become the standard initial evaluation to assess pancreatic disease. As malignancy and other anatomic lesions are relevant to the differential diagnosis, anatomic evaluation

always precedes a functional test of the pancreas for diagnostic purposes. ERCP, endoscopic ultrasound and MRI are other diagnostic tools used in the anatomic assessment of the pancreas. In rare cases of pain or steatorrhea that are not adequately defined by radiographic studies and clinical context, the secretin test may be useful. The difficulties in standardizing and performing the test mentioned by Dr. Garvey remain issues in the value of the secretin test. The diagnostic value in the hands of researchers in the field of pancreatic disease has been accepted in the medical literature. Total volume, total bicarbonate and bicarbonate concentration of the pancreatic fluid are the parameters commonly sited in discussions of the secretin stimulation test. Precise definitions of normal ranges for volume and bicarbonate concentration and quantification of the sensitivity and specificity of the test however are very difficult due to the inter- and intra-variability among both normal subjects and "patients with pancreatic disease". The variability in technique and skill among individuals and centers performing the test is an additional concern. The advisory committee appreciated these points in 1978 and in 1979 when discussing the Secretin-Kabi NDA:

DR. LITTMAN: What I am trying to say is that when you go to do the first study, go to record your data, there are clear cut normals and there are clear cut cancers, clear cut inflammatory disease. When you start using it to solve bedside problems, this was the attack of pain due to pancreatic disease or was it not, that is where tests of this sort begin to strongly attenuate because case ascertainment is weak.

Including laparotomy, I have had to wait five years to find out if somebody had cancer or benign disease, and even then wasn't sure. So, I am trying to say, to come to a useful point, is that I don't think the state of the art permits a highly refined, precise definition of limits, you know, what is pancreatic disease and what isn't.

Our ability to identify the disease clinically is seriously restrained.

DR.HIGHTOWER: Armand, I agree with everything you are saying because in the last thousand cases we have done, they are scattered all over.

DR.LITTMAN: You betcha. And that is not the paper that gets published"

(page 214-215 Advisory committee meeting Dec 12,1978)

DR. ARMAND LITTMAN:

The problem with all research on pancreatic disease is ascertainment. If you do it (secretin test) in a V.A. hospital you have got a lot of alcoholics who probably have had pancreatitis a bunch of times. When you are dealing with suspected disease, how do you prove it? The only way you can be sure that somebody with an irregular contour and malfunction of the pancreas doesn't have cancer is to wait five or ten years.
I am putting this lightly, but this is one of the things that drives good people out of research in this area----proof of the sort we like to have to come out and say these are

result in abnormal instances. The kind of case material we use is not where the problem is.

The burned-out advanced obvious pancreatitis is where a lot of the data come from, and what we need to know and nobody can reliably tell us is how these tests work in patients where there is a doubt, where there is a lot of question." (page 316 GI advisory committee meeting June 1, 1979)

At the other end of the spectrum are patients with normal appearing anatomy of the pancreas on CT scan and endoscopic retrograde pancreatography and an "abnormal" secretin stimulation test. It is difficult to define a clinical entity such as chronic pancreatitis (CP) meaningfully when anatomic and physiologic tests yield differing results. Histologic criteria can add only marginally to the clinical question at hand. The variety of clinical presentations associated with CP complicate attempts to compare the various diagnostic tests available and define a gold standard for diagnosis. The technical difficulties and anticipated variability in the performance of the test in practice further complicate the issue.

Many on the GI Advisory committee expressed concerns over the issue of diagnostic accuracy of the secretin test during discussions of the initial Kabi NDA.

DR. HIGHTOWER:

Any other comments? You know, using the terms of false positive and false negative tests etcetera, I feel a bit uneasy with that. But I mean I know that if you do enough of these tests, they will scatter all over the map. We have suggested that they be given the normal parameter but you see, when you are talking about the test being positive or negative and then you get into a false positive or negative, I don't know how we would determine that.

DR. CONNELL:

I think that you want some expression along the lines that there is a wide overlap between the normal range and the ranges occurring in some disease stage, rather than use the expressions false positive and negative.....

DR. LACHIN:

Would it be helpful to present data on sensitivity and specificity similar to the data that Nick presented earlier? I am talking now true positives and true negatives, not just false positives and negatives.

I think that it might be helpful to know under the best of circumstances what is the diagnostic efficiency of this procedure.....

DR. FARRAR:

Well, I am disturbed that this group that says they want to facilitate the process are getting again into the problem of writing all sorts of package inserts which I think can be irrelevant to the safety and efficacy of this pancreatic stimulant.
And I don't understand why we would give ranges at all. And it seems to me, false positive ranges all of this sort of thing seems irrelevant. But you might give how you give it to stimulate the pancreas, but it seems to me after that you have got to look it up someplace else.

DR. TEMPLE:

But aren't you stimulating it in order to make some determination about what disease the person has and diagnose that?

DR. FARRAR:

Sure.

DR HIGHTOWER:

Well you want to know how the pancreas responds. It will not diagnose chronic pancreatitis or CA. It will not differentiate between those two.

DR.TEMPLE:

Why are you doing it? To fit with other things that will help you diagnose it.

DR. HIGHTOWER:

I think why we do it most often is to try to assess if the patient has pancreatic exocrine insufficiency. That is primarily why we it is done. It is not looking for carcinomas or pancreatitis. Wouldn't you say Frank (Brooks), that is the most often way you would do it?

DR. LITTMAN:

I tried to make the point before that the hard-nosed kind of data you young fellows want and should have are simply not available because ascertainment in that disease doesn't permit precision. The things you want cannot be given unless you could do a thousand tests and determine what disease those thousand people had.
You cannot do that with the pancreas. There are just too many ships that pass in the night. Transitory episodes, patients where you can't distinguish even in surgery between a hardened pancreas due to benign disease or malignant disease. I think that this is what the data suffer from and we all agree this is a useful test because we may pick up a degree of functional impairment that may lead to useful inference.....

DR. KREEK:

Since the values that you get , in other words, normal, abnormal, and the subgroups of abnormal are dependent on the way the test is done in all of its aspects, and since there are a few groups that have done fairly large studies on the past, I think that the best way to facilitate a package insert would simply be to cite secretin is used for such tests, it is to be administered in such and such dose by such and such administration. And that the references are cited one, two, three, four, five, giving specific details as to the way the test is to be performed and the results which are forthcoming when it is performed in that way.

Then you have all the information contained within the package insert that is needed, but it has to be used along with the library. And I think that is the only way. I don't think that there is a way that the secretin test is performed with a set of normal and abnormal values.....

DR.FARRAR:

And I am just telling you that if come in here and if you encourage a very fat one (package insert) we will be here for two or three days. Some may resign. But I don't think we will be able to agree on a right way to interpret a secretin test, Janowitz and Dreiling not withstanding.

DR.CONNELL:

I agree with John (Farrar) that if you look at it in terms of this being a test to diagnose a particular category of disease we would never come to an agreement on how it should be used. However I don't think that there is any disagreement around this table or elsewhere that this test does give you an estimate, as you said, of pancreatic exocrine function, when done well and assessed from the lumen of the duodenum.

Now that seems to me to be the core of what the test does. Everything else is subject to some debate.

DR. HIGHTOWER:

That is why I suggested it The indications for its use might better be, that a specific disease entity that it be exocrine insufficiency of the pancreas because that is primarily why we do it, to assess that particular function.
And you know, then you find out what disease condition you have.....

(page 242-250 GI advisory committee December 12, 1978)

The Review by Dr. T.Q. Garvey reiterated the advisory committees concern over the definition of normal and abnormal secretin tests.

"I am not entirely convinced that gastroenterologists should be encouraged to use the response ranges for volume and maximal bicarbonate concentration described in Kabi's package label to define normalcy. These values are probably close to what might be obtained by experienced investigators in a relatively large series. They appear to be those listed by DiMagno and Co. in a review article. Physicians contemplating secretin testing should however, as emphasized frequently by Dreiling and Grossman, generate their own normal ranges, if only in order to gain experience with the technique."
(Supplementary medical review by Dr. Garvey NDA 18-290 signed 1/29/81)

Ultimately, the current Secretin-Ferring label was written without any statement about sensitivity, specificity or true and false negative or positive results. In fact, the indication is not for diagnosis of a specific disease entity but rather "diagnosis of pancreatic exocrine disease".

However, a reference is cited with a table included in the product label that compared 10 "normal" subjects and 5 patients with "well documented" chronic pancreatitis. This may certainly suggest that the unstated indication is for the diagnosis of chronic pancreatitis.

To further clarify or confuse the reader, the label goes on to state:

"that the cited reference and table are derived from a single study by investigators skilled in performing the secretin test and are to be taken only as guidelines. These results should not be generalized to results of secretin testing in other laboratories. However, a volume response of less than 2.0 ml/kg/hr, bicarbonate concentration of less than 90 mEq/L and bicarbonate output of less than 0.2 mEq/kg/hr are consistent with impaired pancreatic function. A physician or institution planning to perform secretin testing for diagnosis of pancreatic disease should begin by assessing enough normal subjects (≥ 5) to develop proficiency in proper technique and to generate normal response ranges for the three commonly assessed parameters of pancreatic exocrine response to secretin."

The lack of consensus about defining a "normal" and hence an "abnormal' range for the secretin test is reflected in the label.

In order to address this issue, the division requested that the sponsor provide a meta- analysis of the published literature on the accuracy of the SST in the assessment of pancreatic exocrine function. This meta-analysis was submitted on January 28th, 2000 and is reviewed in attachment 2.

Secretin in the diagnosis of gastrinoma (Zollinger Ellison Syndrome/ ZE):

A literature review was the basis for approving Secretin-Ferring for this indication. There was no question that the biologic phenomenon of a paradoxical rise in serum gastrin level in response to an infusion of secretin is unique and typically seen in patients with ZE. The differential diagnosis for this type of response in serum gastrin level following infusion of secretin is limited to ZE.

In the advisory committee and again in the review by Dr. Garvey the relevant issue was defining the diagnostic criteria or cutoff for ZE.

Five studies submitted in the NDA were summarized in Dr. Garvey's review. The studies used various diagnostic criteria for ZE as well as varying dosages and products (Boots and GIH). Among healthy subjects 0/46 showed a rise in gastrin of 110 pg/ml or greater. Among patients with duodenal ulcer but no suspicion of ZE 0/49 had a diagnostic rise in gastrin.

Among patients with "proven" ZE (histology or persistently elevated gastrin s/p gastrectomy) 37/37 had a positive secretin test.

In the gray zone of suspected but unconfirmed cases of ZE the data were not clear. The reviewer concluded that:

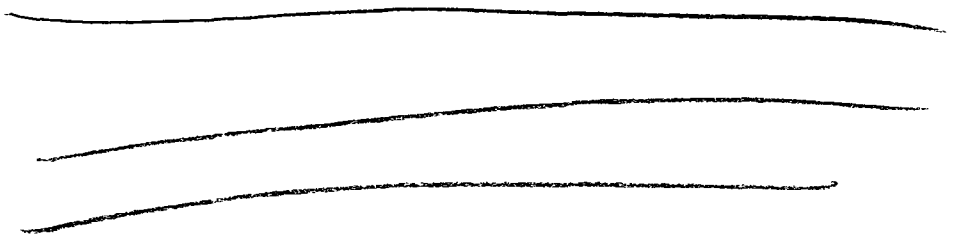
"The data from the five studies summarized above provide substantial evidence that assessment of GIH (Kabi product) secretin stimulated serum gastrin response in patients with suspected gastrinoma is a powerful diagnostic technique. Using 0.2 μg/kg of secretin and an antibody for the gastrin RIA similar or identical to that prepared by Rehfeld and used by Deveny et al, Lamer et al. and Mihas et al.; an increment in fasting gastrin of 110 or more pg/ml above the basal level at 5 min after administration of secretin is presumptive evidence of Z-E Syndrome. A response of less than 110 pg/ml makes the diagnosis extremely unlikely." (Page 22 of review)

An article by McGuigan and Wolfe in 1980 reviewed the published literature to date[2]. The authors discussed several reports in which the secretin test was found to be less accurate in diagnosing ZE than the studies in the NDA 18-290 submission. These authors pointed out the differences in secretin product (Boots versus GIH), dose, method of infusion, timing of serum sampling, and criteria for diagnosis in the studies. These differences were felt to be the source of inaccuracy of the test in the cited reports. The authors specifically state that:

"At the present time there is insufficient information in the literature to compare secretin provocation results using the several available forms of synthetic porcine secretin with the with results using the purified naturally occurring porcine secretins." [2]

It is worth noting at this point that the synthetic porcine secretin is significantly different than the GIH/Kabi natural purified product. The natural product contains [redacted] impurities according to the sponsor. These impurities are not characterized. They may represent biologically active gut hormones that may contribute to the gastrin releasing effect seen in the secretin test. Gastrin RIA crossreactivity with these peptides cannot be ruled out. The cautious note in the McGuigan and Wolfe article about the need for experience with the synthetic product is therefore quite relevant to the current NDA.

2 Page(s) Withheld



4.3 Foreign Experience

Synthetic porcine secretin has not been marketed outside the United States.

4.4 Human pharmacology, Pharmacokinetics, Pharmacodynamics

The current NDA does not include primary source pharmacokinetic data. Literature from experience with the biologically derived and less pure product as well as non-sponsor synthetic secretin is referenced. In the article on biologically derived secretin a one-compartment model was found to best describe the kinetics of secretin. $T_{1/2}$ in that study was approximately 4 minutes.[3] The clearance rate was approximately 540 ml/min.[3] Protein binding in human plasma was reported to be 40%.
A referenced study using a synthetic product other than the sponsor's showed a $T_{1/2}$ of approximately 3 minutes.[4]

The pharmacodynamics of secretin is the subject of the only original studies in the current NDA. These data will be reviewed in subsequent sections. The sponsor's development design was to compare the approved BPS and the SPS in terms of the three pharmacodynamic parameters: pancreatic juice volume, bicarbonate concentration and total bicarbonate. These comparative data form the basis for efficacy claims regarding the sponsor's synthetic secretin product's value as a diagnostic tool for pancreatic exocrine disease. Table 2 shows pharmacodynamic data using the currently approved biologic porcine secretin product in the hands of other laboratories over the past 30 years.

Table 2 PK of Porcine derived secretin in healthy volunteers :All GIH/Kabi product

Source of Information	Volume	Peak Bicarbonate	Total Bicarbonate
(ml/kg) ConcentrationDreiling 1955 [5]- Normal subjects— rates over 80 min (1 CU/kg) results expressed as 2S.D. (? Slow infusion or bolus)	2.0-4.4	90-130 mEq/L	12.2-31 mEq
Petersen [6]-- Normal subjects (rates over 60 minutes after injection of 1CU/kg) (Female n=11 Male n=15)	Males Range 2.3-5.7 Mean: 3.8 ± 0.9 Females Range 2.6-5.2 Mean3.6 ±0.8	males: Range 90-124 Mean 103± 9 Females: Range 88-116 mMan101± 9	**Total mEq** Males Range13-42 Mean· 25± 7 Females Range 12-27 Mean 19±5 **mEq/kg** Males Range 0.17-0 58 Mean 0.34± 0. Females Range 0.22-0.55 Mean 0.32± 0 07
Gutierrez and Baron [7] Normal subjects (rates over 60 minutes after injection of 1CU/kg) (n=10)	Range 2.7-4.0 Mean 3.6± 0.8	Range 90-141 Mean 114± 20	

4.5 Directions for use in pancreatic function testing:

The sponsor proposes using near identical instructions compared to the current label for Secretin-Ferring. The only difference is the recommendation that the pancreatic juice collections be in 4 equally timed 15 minute collection periods rather than the 2 ten minute and 2 twenty minute periods noted in the current label of Secretin –Ferring.

2 Draft Labeling Page(s) Withheld

[redacted]

5 Description of Clinical Data Sources

5.1 Study type and design/patient enumeration, demographics, extent of exposure

The sponsor has submitted five clinical studies in support of the NDA.

1. CRC 97-1: This was a pharmacodynamic dose ranging study of 12 healthy subjects. The goal was to find the dose that produces maximal pancreatic stimulation and to compare the different doses to the currently approved dose of Ferring Secretin for the indication of pancreatic exocrine function. Variability in response in healthy subjects was assessed as well. Safety data were also collected.

2. CRC 97-2 This is an ongoing open label study of secretin usage for multiple indications including [redacted] gastrinoma and technically difficult ERCP cannulation. At the time of submission, there were no positive secretin tests from gastrinoma.

   A supplemental pre-meeting packet received on September1, 1999 updating the open label experience:

   a. Ten patients were given the sponsor's synthetic porcine secretin (SPS) for the indication of "assisting in ERCP cannulation" (eight cases for minor papilla cannulation). All ten had successful cannulation of both minor and major