CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

PHARMACOLOGY REVIEW(S)

PHARMACOLOGIST'S REVIEW OF NDA 21, 209 and 21, 136
[Amendments Dated February 13, 2002]

Sponsor & Address: ChiRhoClin, Inc.
Silver Spring, MD.

Reviewer Name: Tamal K. Chakraborti, Ph.D.
Pharmacologist, HFD-180

Date of Submission: February 13, 2002

Date of HFD-180 Receipt: February 14, 2002

Date of Review: March 5, 2002

Drug: Synthetic Porcine Secretin lyophilized Sterile Powder 16 µg Intravenous Injection.

Category: Diagnostic.

Submission Contents:

1. Draft labeling.

LABELING: The labeling of NDA 21, 209 and 21, 136 are same and therefore, both the amendments are reviewed here. This is sponsor's version in response to the Division's recommended version dated May 16, 2000. The draft labeling of synthetic porcine secretin conforms to the format specified under CFR 21, subpart B, 201.5 to 201.57 dated April, 1998. However, the following changes should be made in the proposed labeling:

Proposed Labeling:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility:

Previously Recommended Version:

"Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of —— ecretin. Studies to evaluate the possible impairment of fertility or mutagenic potential ——
—— have not been ——

Sponsor's Version:

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of [redacted] secretin.

Reviewer's Comments:

The second sentence [redacted] is unnecessary and should be deleted.
Therefore the above stated changes should be incorporated in the proposed labeling as recommended below.

Recommendation: The proposed text of sponsor should be modified as stated below:

Final Version:

"Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of [redacted] secretin. Studies to evaluate its potential for impairment of fertility or its mutagenic potential have not been [redacted]

2. **Pregnancy. Teratogenic Effects.**

Previously Recommended Version:

"Pregnancy Category C: Animal reproduction studies have not been conducted with [redacted] secretin. It is also not known whether [redacted] secretin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. [redacted] secretin should be given to a pregnant woman only if clearly needed."

Sponsor's Version:

Pregnancy Category C: Animal reproduction studies have not been conducted with secretin. It is also not known whether secretin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. secretin should be given to a pregnant woman only if clearly needed.

Reviewer's Comments: According to CFR 21, subpart B, 201.5 to 201.57, the subsection "Pregnancy. should be incorporated in the labeling.

Recommendation: The proposed text of sponsor should be modified as stated below:

Final Version:

"**Pregnancy. Pregnancy Category C:** Animal reproduction studies have not been conducted with secretin. It is also not known whether secretin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. secretin should be given to a pregnant woman only if clearly needed."

3. **Nursing Mothers:**

Previously Recommended Version:

"**Nursing Mothers:** It is not known whether secretin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when secretin is administered to a nursing woman."

Sponsor's Version:

Nursing Mothers: It is not known whether secretin is excreted in human milk. Because many drugs are excreted in human milk, caution is advised when is administered to a nursing woman.

Reviewer's Comments: In the first sentence should be added before the word "secretin".

Therefore the above stated changes should be incorporated in the proposed labeling as recommended below.

Recommendation: The proposed text of sponsor should be modified as stated below:

"**Nursing Mothers:** It is not known whether — secretin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when — secretin is administered to a nursing woman."

4. OVERDOSAGE:

Previously Recommended Version:

"**Overdosage:** Single intravenous dose of 20 µg/kg of synthetic porcine secretin was not lethal to mice or rabbits".

Sponsor's Version:

OVERDOSE

A single intravenous dose of 20µg/kg of synthetic porcine secretin was not lethal to mice or rabbits.

Reviewer's Comments: "Overdose" should be changed to "OVERDOSAGE".

Recommendation: The proposed text of sponsor should be modified as stated below.

Final Version:

"OVERDOSAGE

Single intravenous dose of 20 µg/kg of synthetic porcine secretin was not lethal to mice or rabbits."

SUMMARY AND EVALUATION:

In this submission, the sponsor submitted the draft labeling in response to Division letter dated January 28, 2002 asking the sponsor to provide draft labeling for synthetic porcine secretin.

The necessary changes with specific recommendations are provided in the text of the review.

RECOMMENDATION:

Sponsor should be asked to change the proposed label of Synthetic Porcine Secretin as suggested in the text of the review.

/S/

Tamal K. Chakraborti, Ph.D. Date
Pharmacologist, HFD-180

Comment:

/S/

Jasti B. Choudary, B.V. Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

Cc:
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakraborti
HFD-180/Dr. Choudary

R/D Init. : J. Choudary 3/5/02

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Tamal Chakraborti
3/5/02 01:28:33 PM
PHARMACOLOGIST

Jasti Choudary
3/5/02 01:38:02 PM
PHARMACOLOGIST

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ON ORIGINAL

Strongin

MAR 29 2000

PHARMACOLOGIST'S REVIEW OF NDA 21, 136
[Amendment Dated December 29, 1999 (# B2)]

Sponsor & Address: ChiRhoClin, Inc.
Silver Spring, MD.

Reviewer Name: Tamal K. Chakraborti, Ph.D.
Pharmacologist, HFD-180

Date of Submission: December 29, 1999

Date of HFD-180 Receipt: December 30, 1999

Date of Review: March 28, 2000

Drug: Synthetic Porcine Secretin lyophilized Sterile Powder 16 µg Intravenous Injection.

Category: Diagnostic.

Submission Contents:

1. Biological Assay for Potency Stability on Synthetic Porcine Secretin Lot Numbers: 78104, 92704C, and 927-5.

Biological Assay for Potency Stability on Synthetic Porcine Secretin Lot Nos. 78104, 92704C, and 927-5

The biological activity of synthetic porcine secretin was assessed using a domestic short hair cat (7 months of age and weighing 3.8 kg upon receipt). A soft tubing was introduced into the stomach through a small incision to allow evacuation of gastric juice. Another tubing was also introduced into the jejunum through a small incision to allow introduction of solutions (nutrients and anesthesia, etc.). The pancreatic duct was cannulated. Synthetic secretin or the reference standard, Ferring Secretin, was administered via intravenous (i.v.) injection via the cephalic vein. The pancreatic juice was collected after each injection into a small vessel containing 2 ml of 0.1M hydrochloric acid (HCl) with a pH color indicator added. The HCl-pancreatic juice solution was boiled and then titrated with 0.1 M sodium hydroxide (NaOH). The amount of bicarbonate in the pancreatic juice was calculated by subtracting the amount of NaOH required to titrate the HCl-pancreatic juice solution (2.0 ml) and multiplying by 100.

The potencies of ChiRhoClin's Synthetic Porcine Secretin, Lot Nos. 78104, 92704C, and 927-5 were — , respectively, biologically active compared to Ferring Secretin (Lot No. ZL 5511A). Assuming 2µg/ml of Synthetic Porcine Secretin = 10 CU/ml Ferring Secretin: 1µg = 5CU. Based upon the results of the biological assay, 1 µg = ... — or Lot Nos. 78104, 92704C, and 927-5, respectively. Clinical Unit (CU) is defined as follows: 1 Clinical Unit = 20 HCU (Hammarsten

Cat Unit; Jorpes JE and Mutt V. 1966. On the biological assay of secretin. The reference standard. *Acta Physiol. Scand.* 66: 316-325; Heatley NG. 1968. The assay of secretin in the rat. *J. Endocrinol*. 42: 535-547). The Hammarsten Cat Unit is defined as the amount of secretin, which in the cat induces secretion of 0.1 ml of 0.1 N bicarbonate in the 15-min period following injection (Jorpes JE and Mutt V. 1966. On the biological assay of secretin. The reference standard. *Acta Physiol. Scand.* 66: 316-325).

SUMMARY AND EVALUATION:

Secretin is a gastrointestinal peptide (27 amino acid) hormone secreted from duodenum when the pH of the duodenal content is less than 4.5. The physiologic function of secretin is to stimulate the exocrine pancreas gland to secrete pancreatic juice containing high amount of bicarbonate and water. The sponsor in the New Drug Application (NDA 21, 136), proposed to use Synthetic Porcine Secretin (sPS) in the diagnosis of pancreatic dysfunction (at 0.2 µg/kg by intravenous injection over 1 minute), ———————————————————————————————————, in suspected gastrinoma (Zollinger-Ellison Syndrome at 0.4 µg/kg by intravenous injection over 1 minute) and for the facilitation of pancreatic duct cannulation during ERCP (endoscopic retrograde cholangiopancreatography at 0.2 µg/kg by intravenous injection over 1 minute). The sponsor has previously submitted report of biological assay for potency (— biologically active compared to Ferring Secretin, Lot No. 4584) on sPS (sPS 36742, Batch 698, Lot No. 03672).

In this submission, the sponsor submitted a report of biological assay for potency on synthetic porcine secretin Lot Nos. 78104, 92704C, and 927-5.

The bioassay of synthetic porcine secretin (sPS) was done by using one domestic short hair male cat. The potencies of ChiRhoClin's Synthetic Porcine Secretin, Lot Nos. 78104, 92704C, and 927-5 were — and — respectively, biologically active compared to Ferring Secretin (Lot No. ZL 5511A). Based upon the results of the biological assays, 1 µg of sPS was found to be equivalent to —, and — CU for Lot Nos. 78104, 92704C, and 927-5, respectively. The sponsor has previously submitted report of biological assay for potency — % biologically active compared to Ferring Secretin, Lot No. 4584) on sPS (sPS 36742, Batch 698, Lot No. 03672) and based on the results of the biological assay, 1 µg of sPS (sPS 36742, Batch 698, Lot No. 03672) was reported to be equivalent to —. CU.

RECOMMENDATION: None.

[/S/]
Tamal K. Chakraborti, Ph.D. 3/28/00
Pharmacologist Date

Comment: None
[ ] 3/29/00
Jasti B. Choudary, B.V.Sc.,Ph.D. Date
Pharmacology Team Leader

cc:
NDA: 21,136
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakraborti
HFD-180/Dr. Choudary

R/D Init. : J. Choudary: 3/27/00
TC/deg: 3/28/00
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ON ORIGINAL

SEP 16 1999

SPONSOR & ADDRESS: ChiRhoClin, Inc.
Silver Spring, MD.

REVIEWER: Tamal K. Chakraborti, Ph.D.
Pharmacologist

DATE OF SUBMISSION: May 14, 1999

DATE OF HFD-180 RECEIPT: May 26, 1999

DATE OF REVIEW: September 10, 1999

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

DRUG: Synthetic Porcine Secretin Lyophilized Sterile Powder 16 μg Intravenous Injection.

CHEMICAL NAME AND 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

MOLECULAR FORMULA: $C_{130}H_{220}N_{44}O_{41}$

MOLECULAR WEIGHT: 3055.5

FORMULATION: Synthetic porcine secretin is supplied as a lyophilized sterile powder in 10 ml vials. Each 10ml vial contains: 16 μg Synthetic porcine secretin (free powder base), 15 mg L-Cysteine hydrochloride monohydrate, and 20 mg Mannitol USP. When reconstituted in 8.0ml of Sodium Chloride Injection USP, each ml of the solution contains 2 μg secretin for intravenous use. The pH of the reconstituted solution has a range of 3.0-6.5.

CATEGORY: Diagnostic.

RELATED DRUGS/INDS/NDAs/MFs: IND 54, 196 (Synthetic Porcine Secretin, ChiRhoClin, Inc.). NDA 18-290 (Biologically derived porcine secretin, Ferring).

MARKETING INDICATION: Synthetic porcine secretin is indicated for the diagnostic use in pancreatic dysfunction, ——————————, in suspected gastrinoma ——— and for the facilitation of ——— during endoscopic retrograde cholangiopancreatography (ERCP).

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DOSE:

[redacted]

2. Diagnosis of gastrinoma ([redacted]): 0.4 μg/kg body weight by intravenous injection over 1 minute.

3. Facilitation of [redacted] during ERCP: 0.2 μg/kg body weight by intravenous injection over 1 minute.

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of Study	Study #	Drug Lot #	Laboratory	Review Page #
I. PHARMACOLOGY				3
II. TOXICOLOGY				
A. Acute Toxicity				
1. Acute Toxicity Study in Mice	[redacted]700449	78104	1	7
2. Acute Toxicity Study in Rabbit	[redacted]700450	78104	1	7
B. Subacute Toxicity				
1. 14-Day Intravenous Toxicity Study in Rats	98-2603	78104	2	8
2. 14-Day Intravenous Toxicity Study in Dogs	98-3385	78104	2	10

1 = [redacted]
2 = [redacted]

The following studies were previously submitted to IND 54, 196 (Amendment # 002 dated February 21, 1998): (1) Biological assay for potency on synthetic porcine secretin, and (2) Acute toxicity in mice and rabbits. These studies were reviewed earlier (Pharmacology review of IND 54, 196 dated March 9, 1998). These reviews are incorporated in the appropriate portion of the present review. In addition, new studies submitted in the present NDA have been reviewed below.

PHARMACOLOGY:

Secretin is a gastrointestinal peptide (27 amino acid) hormone secreted from duodenum when the pH of the duodenal content is less than 4.5. The physiologic function of secretin is to stimulate the exocrine pancreas gland to secrete pancreatic juice containing high amount of bicarbonate and water. In this way, it flushes out pancreatic digestive enzymes into the duodenum and causes alkalization of the duodenum content and provides optimal chemical environment (in terms of pH) for the biological activity of pancreatic enzymes (pancreatic amylase, proteolytic and lipolytic). Its pharmacological activities were characterized in a number of *in vitro* and *in vivo* preparations as reported in several scientific publications. Its usefulness as a preferred diagnostic agent in pancreatic dysfunction such as chronic pancreatitis, Zollinger-Ellison Syndrome (ZES) and in discriminating between ZES and duodenal ulcer has been discussed below.

A. Primary Pharmacological Activity related to the Proposed Diagnostic Uses

1. Primary Pharmacological Properties:

The key pharmacological properties of secretin (Leiter BA, Chey WY, and Kopin AS. *Gut Peptides: Biochemistry and Physiology*, edited by J. H. Walsh and G. I. Dockray. New York: Raven Press, Ltd., 1994, p 147-173) are shown in the following table:

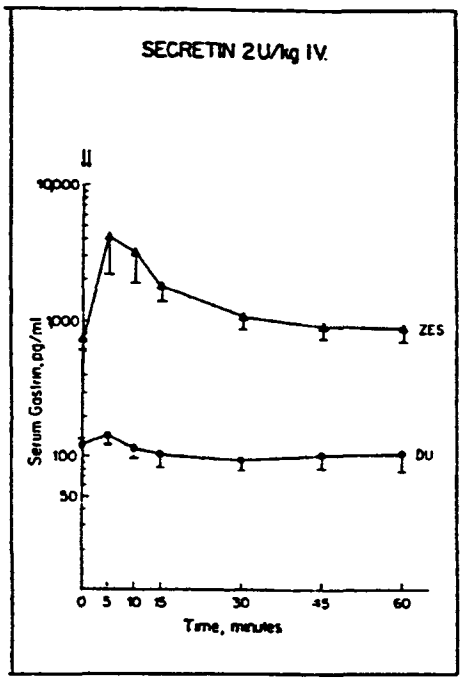
TABLE 1. *Release and actions of secretin*

Release	Action
Acid	
nonacid stimulants	*Stimulation*
Bile Salts	Pancreatic secretion of fluid and HCO_3[c]
Oligopeptide[a]	Biliary Secretion of Fluid and HCO_3
Long Chain Fatty Acid	Gastric Pepsinogen
Sodium Oleate	Gastric Mucus
Herbal Extracts	Brunner's Glands
curcuma longa	Endocrine Pancreas
licorice root	Insulin, Glucagon, Somatostatin
plasma	Growth: pancreas
	Inhibition
	Gastric Acid Secretion[c]
	Gastrin release[c]
	Gastrointestinal motility
	LES[b], Stomach[c], Intestine, Colon
	Growth
	Gastric mucosa

[a] In rats only
[b] Lower esophageal sphincter
[c] Physiological action

The major stimulant for secretin release was found to be acid, in fact, the pH threshold for the release of secretin was shown to be 4.5 in the duodenum of the dog. The release of secretin was abolished by cimetidine, a H_2 receptor antagonist. However, oxethazine, somatostatin, and Met-enkephalin caused inhibition of secretin release. Secretin increases pancreatic secretion of water and bicarbonate at a physiological dose (0.03 Clinical Unit or CU/kg/hr) in mammalian species, including humans, dogs and rats. It causes inhibition of pentagastrin-induced acid secretion and gastrin release. Secretin suppresses the release of gastrin in response to a meal in normal and in patients with duodenal ulcer disease. Interestingly, secretin causes elevation of gastrin release

from tumor tissues in patients with Zollinger-Ellison Syndrome (ZES). Secrtin was found to increase gastrin release (4, 063 ± 1, 990 pg/ml) in patients with ZES (Mihas AA, Hirschowitz BI, and Gibson RG. Calcium and secretin as provocative stimuli in the Zollinger-Ellison Syndrome. *Digestion* 17: 1-10, 1978). In contrast, in duodenal ulcer patients, secretin caused a progressive fall in serum gastrin level (from 119 to 97 pg/ml).



Above figure (from Vol. 1.1, page 338 of sponsor's submission) shows the effect of secretin on serum gastrin level of patients with duodenal ulcer and ZES.

This differential effect of secretin on gastrin release in duodenal ulcer patients (decrease in gastrin release) and patients with ZES (increase in gastrin release) may be of diagnostic importance (Thompson JC, Reeder D, Bunchman HH, Becker HD, and Brandt EN. Effect of Secretin on Circulating Gastrin. *Annual Meeting of the American Surgical Association*, April 26-28, 1972, San Francisco, California).

2. <u>Secretin Dose-Response in Health and Chronic Pancreatic Inflammatory Disease:</u>

This study (Petersen H. and Myren J. Secretin dose-response in health and chronic pancreatic inflammatory disease. *J. Gastroent.* 10: 851-861, 1975) was designed to examine the sensitivity to secretin in pancreatic inflammatory disease compared to healthy human volunteers. Secretin was administered in stepwise increasing doses (0.078-2.1 U/kg/hr) to healthy volunteers and patients suffering from pancreatic inflammatory disease for more than 5 years (CP5) and two years or less (CP2).

Bicarbonate response was found to be lower in the majority of CP5 and 1/3rd of CP2 patients. Mean Vmax (maximal bicarbonate response) values were 22.3, 19.2 and 9.7 mEq/30 min in healthy volunteer (HV), CP2 and CP5, respectively. The corresponding peak values were 18.6, 18.2 and 7.8 mEq/30 min. The doses of secretin required for half maximal bicarbonate response (Km) were 0.40 U/Kg-h in HV and 0.23 and 0.53 U/Kg-h in CP2 and CP2, respectively. However, the results suggested that the bicarbonate/calcium ratios were invariably lowered in these patients compared to the healthy volunteers suggesting diagnostic superiority to bicarbonate.

3. **Function Tests in the Diagnosis of Pancreatic Dysfunction:**

The pancreatic function test was developed based on the fact that if the pancreatic secretory cells are damaged or in any way impaired in their function, the deficiency should be revealed if the gland's secretory capability is compared to normal in response to a stimulus (which will elicit a maximal secretory response). Direct stimulation of pancreas by secretin and the measurement of the concentration and volume of bicarbonate (80-150 mM/l in pancreatic juice from normal subjects) were considered to be a reliable technique in examining the pancreatic function (Scratcherd T. Symposium on diagnosis of pancreatic disease. Pancreatic function tests: The physiological background. *Gut* 16: 648-663, 1975). Secretin test was also used to diagnose pancreatic cancer. The diagnostic accuracy of the standard secretin test for pancreatic cancer was tested in 5,000 cases and the accuracy range was found to be around 90% which is shown in the following table (reproduced from Vol. 1.1, page 254 of sponsor's submission):

Disease State	Total No.	No. of Errors	Percentage of Errors
No Pancreatic Disease	2725	139	5.1
Proved Pancreatic Disease	1818	93	5.2
Indeterminate Cases	500	250	50
Total Series	5043	482	9.6

The effects (% increase) of an augmented secretin test (4.0 CU/kg, compared to normal secretin test at 1.0 CU/kg) on the discriminative parameters in normal condition, in patients with chronic pancreatitis and patients with pancreatic cancer are shown below (reproduced from Vol. 1.1, page 256 of sponsor's submission):

Parameter	Normal	Chronic Pancreatitis	Pancreatic Cancer
Bicarbonate Flow	100%	40%	15% or Fixed
Bicarbonate Conc.	15%	Fixed or Decreased	10%

Literature evidences (Lankisch PG. Function tests in the diagnosis of chronic pancreatitis. *International Journal of Pancreatology* 14: 9-20, 1993) suggests that direct pancreatic function tests (Secretin and Lundh test) are the best way to assess exocrine pancreatic function but these tests are time-consuming, invasive and expensive. Although indirect pancreatic function tests are available alternative; however, these tests do not provide any information regarding the etiology or help to differentiate between pancreatic insufficiency due to chronic pancreatitis and pancreatic cancer.

B. Biological Assay for Potency on Synthetic Porcine Secretin

The biological activity of synthetic porcine secretin was assessed using a domestic short hair cat (8 months of age and weighing 3.8 kg upon receipt). A soft tubing was introduced into the stomach through a small incision to allow evacuation of gastric juice. Another tubing was also introduced into the jejunum through a small incision to allow introduction of solutions (nutrients and anesthesia, etc.). The pancreatic duct was cannulated. Synthetic secretin or the reference standard, Ferring Secretin, was administered via intravenous (i.v.) injection via the cephalic vein. The pancreatic juice was collected after each injection into a small vessel containing 2 ml of 0.1M hydrochloric acid (HCl) with a pH color indicator added. The HCl-pancreatic juice solution was boiled and then titrated with 0.1 M sodium hydroxide (NaOH). The amount of bicarbonate in the pancreatic juice was calculated by subtracting the amount of NaOH required to titrate the HCl-pancreatic juice solution (2.0 ml) and multiplying by 100.

The potency of ChiRhoClin's Synthetic Porcine Secretin 36742, Batch 698, Lot No. 03672 was — biologically active compared to Ferring Secretin (75 CU/vial, Lot No. 4584). Assuming 2μg/ml of Synthetic Porcine Secretin = 10 CU/ml Ferring Secretin: 1μg = 5CU. Based upon the results of the biological assay, 1 μg = — CU. Clinical Unit (CU) is defined as follows: 1 Clinical Unit = 20 HCU (Hammarsten Cat Unit; Jorpes JE and Mutt V. 1966. On the biological assay of secretin. The reference standard. *Acta Physiol. Scand.* 66: 316-325; Heatley NG. 1968. The assay of secretin in the rat. *J. Endocrinol.* 42: 535-547). The Hammarsten Cat Unit is defined as the amount of secretin, which in the cat induces secretion of 0.1 ml of 0.1 N bicarbonate in the 15-min period following injection (Jorpes JE and Mutt V. 1966. On the biological assay of secretin. The reference standard. *Acta Physiol. Scand.* 66: 316-325).

TOXICOLOGY:

Acute Toxicity

1. Acute Toxicity Studies in Mice and Rabbits (QT9700449)

Report No.	Testing Laboratory	Species & Route	Date Started	Date Completed	Batch #
— 9700449	1	Swiss Webster Mice	Not provided	January 27, 1998	78014
— 9700450	1	New Zealand White Rabbits	Not provided	January 27, 1998	78104

1 = ———

GLP Compliance: A statement of compliance with the GLP regulations and Quality Assurance Unit was not included.

Methods: The acute toxicity of Synthetic Porcine Secretin (sPS) was examined in mice (5/sex/ group) and rabbits (2/sex for secretin and 1/sex for control) by i.v. route of administration at a dose of 20 μg/kg. The control animals received physiological saline. Body weights were recorded at the end of the quarantine period, just prior to dosing and at the end of the observation period. Animals were observed for clinical signs of toxicity and moribundity/mortality immediately following the treatment and at 1, 2, 4, 24, 48 and 72 hr after dosing. Animals were sacrificed for gross examination. For each animal, the external surface of the body, all orifices, the cranial, thoracic, abdominal cavities were examined. Gross examinations of the following organs and tissues were performed: adrenal glands, brain, esophagus, heart, kidneys, lungs, ovaries, peripheral nerves, preputial/clitoral, skeletal muscle, spleen, testes, tongue, uterus, aorta, cervix/vagina, eyes, large intestine (cecum, colon, rectum), larynx/pharynx, lymph nodes (mandibular, mesenteric), oviducts, pituitary gland, salivary gland, skin, sternum, thymus, trachea, gross lesions, bone marrow, epididymides, femur, small intestines (duodenum, ileum, jejunum), liver, mammary gland, pancreas, prostrate gland, seminal vesicles, spinal cord, stomach, thyroid/parathyroid, urinary bladder and tissue masses.

Results: There was no mortality or clinical signs of toxicity in mice or rabbits at 20 μg/kg of sPS. There were no significant gross pathological changes in either mice or rabbits.

Acute Toxicity of Synthetic Porcine Secretin in Mice and Rabbits

Species	Route	Dose, μg/kg	Maximum Non-Lethal Dose, μg/kg		Minimum Lethal Dose, μg/kg		LD-50, μg/kg		Time to Death
			Male	Female	Male	Female	Male	Female	
Mice	i.v.	20	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Rabbit	i.v.	20	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

N.D. = Not determined.

In acute toxicity studies with mice and rabbits, animals were treated with sPS at 20 μg/kg intravenously. There was no mortality or clinical signs of toxicity. There were no significant gross pathological changes in either species.

Subacute Toxicity

14-Day Intravenous Toxicity Study with Porcine and Human Secretin in Rats (Study No. 98-2603)

Testing Laboratory: [redacted]

Date of Study Initiation: November 24, 1998

Date of Study Completion: April 27, 1999

GLP and QAU Compliance: A statement of compliance was included.

Animals: Sprague Dawley Rats
Male: 154-200 g, 6 weeks old
Female: 134-177 g, 6 weeks old

Drug Batch No. : 78104

Methods: To evaluate the toxicity of synthetic porcine secretin (sPS) and human secretin in rats, rats (10/sex/group) were administered with sPS at 0 (Group I), 0.4 (Group II) and 10 (Group III) and human secretin at 0.4 (Group IV) and 10 (Group V) μg/kg/day for 2 consecutive weeks by intravenous (bolus) administration. The basis of dose selection was not mentioned. The concentrations of drug solutions were 2 μg/ml. The dose volumes for Group I and Group III and Group V were 5 ml/kg and for Group II and Group IV were 0.2 ml/kg. Control animals received vehicle (mannitol, L-Cysteine hydrochloride in 0.9% saline) at a dose volume of 5 ml/kg. Animals were observed twice daily for clinical examinations and for morbidity/ mortality checks. Body weight was recorded twice pretest, weekly during treatment and terminally just prior to necropsy. Food consumption was measured once weekly beginning one week prior to treatment. Clinical pathology (hematology and blood chemistry) was performed at termination. All animals were necropsied at termination and organs (adrenal glands, thoracic aorta, bone, bone marrow, brain, epididymis, esophagus, eyes, heart, injection site, kidneys, lacrimal glands, large intestine, liver, lungs, lymph nodes, mammary glands, muscle (bicep femoris), nerve (sciatic), ovaries, pancreas, pituitary gland, prostate gland, salivary glands, seminal vesicles, skin, small intestine, spinal cord, spleen, stomach, testes, thymus, thyroid, trachea, urinary bladder, uterus, vagina, etc.) were weighed. Histopathological examinations were done on above-mentioned organs for all animals in the control and high dose groups. The pancreas was examined for all animals in Groups II and III.

Results:

1. Observed Effects: No treatment-related clinical signs were observed in any dose group.

2. Mortality: None.

3. Body Weight: The mean initial and final body weights of control males were 107.9 g and 262.3 g, respectively. The mean initial and final body weights of control females were 109.8 g and 200.8 g, respectively. There were no treatment-related changes of body weights following administration of either sPS or human secretin.

4. Food Consumption: The mean initial and final food consumptions of control males were 150.5 g/kg/day and 97.2 g/kg/day, respectively. The mean initial and final body weights of control females were 135.2 g/kg/day and 93.5 g/kg/day, respectively. There were no treatment-related effects on the food consumption following administration of sPS. However, a statistically significant increase in food consumption during week-2 was observed in males treated with 0.4 (107% of control) or 10 (106% of control) μg/kg/day of human secretin compared to control.

5. Hematology: There were no treatment-related effects following administration of sPS or human secretin.

6. Blood Chemistry: Statistically significant reduction (9.8%) in glucose level in females treated at 0.4 μg/kg/day of sPS compared to control (162 mg/dL). This observation was not dose-related and not considered treatment-related. About 10% increase in potassium levels was seen in males at 10 μg/kg/day compared to control (6.0 mEq/L) and this increase was also not considered drug-related because the changes were considered too small in magnitude to be physiologically relevant. There were no treatment-related effects observed on clinical chemistry parameters in either sex following treatment with 0.4 or 10 μg/kg/day of human secretin.

7. Organ Weights: About 17% reduction in the organ to body weight ratio (0.0188/205 = 9.17) for the thyroid and parathyroid gland was observed in the females at 10 μg/kg/day compared to control (ratio = 0.0222/201 = 11.04). All other organ weight data was found similar to control.

8. Gross Pathology: There was no macroscopic findings related to treatment.

9. Histopathology: There was no microscopic findings related to treatment (sPS or human secretin), however, microscopic findings (congestion, necrosis, perivascular soft tissue hemorrhage or inflammation or fibrosis at tail) at the injection site (tail) was found sporadically and considered to be due to injection procedure. Minimal pancreatic acinar cell atrophy was seen in 1/10 male rats in group III, IV and V.

There was no significant adverse effect of synthetic porcine secretin or human secretin at 0.4 or 10 μg/kg dose levels in rats. The no observed effect levels (NOEL) for sPS and human secretin were in Sprague-Dawley rats appeared to be 10 μg/kg/day and no organ of toxicity could be identified because of the lack of adverse effects at these dose levels.

14-Day Intravenous Toxicity Study with Porcine and Human Secretin in Dogs: (Study No. 98-3385)

Testing Laboratory: [ ]

Date of Study Initiation: January 18, 1999

Date of Study Completion: April 29, 1999

GLP and QAU Compliance: A statement of compliance was included.

Animals: Beagle Dogs
Male: 7.2-8.5 kg, approximately 5 months old
Female: 6.3-7.9 g, approximately 5 months old

Drug Batch No.: 78104.

Methods: To evaluate the toxicity of synthetic porcine secretin (sPS) and human secretin in dogs, animals (3/sex/group) were administered with sPS at 0 (Group I), 1.5 (Group II) and 5 (Group III) μg/kg/day and human secretin at 1.5 (Group IV) and 5 (Group V) μg/kg/day for 2 consecutive weeks by intravenous (bolus) administration. The sponsor did not provide the basis of dose selection. The concentrations of drug solutions were 2 μg/ml. The dose volumes for Group I and Group III and Group V were 2.5 ml/kg and for Group II and Group IV were 0.75 ml/kg. Control animals received vehicle (mannitol, L-Cysteine hydrochloride, and sodium bicarbonate in 0.9% saline) at a dose volume of 2.5 ml/kg. Animals were observed twice daily for viability checks and twice pretest and once weekly during the study period for clinical examinations. Body weight was recorded twice pretest, weekly during treatment and terminally just prior to necropsy. Visual examination of food consumption was made four times per week prior to study initiation and seven times a week throughout the study period. Clinical pathology (hematology and blood chemistry) was performed at pretest and termination. All animals were necropsied at termination and organs (adrenal glands, thoracic aorta, bone, bone marrow, brain, epididymis, esophagus, eyes, heart, injection site, kidneys, lacrimal glands, large intestine, liver, lungs, lymph nodes, mammary glands, muscle (bicep femoris), nerve (sciatic), ovaries, pancreas, pituitary gland, prostate gland, salivary glands, seminal vesicles, skin, small intestine, spinal cord, spleen, stomach, testes, thymus, thyroid, trachea, urinary bladder, uterus, vagina, etc.) were weighed. Histopathological examinations were done on above-mentioned organs for all animals in the control and high dose groups. The pancreas was examined for all animals in Group II.

Results:

1. Observed Effects: No treatment-related clinical signs were observed in any dose group.

2. Mortality: None.

3. Body Weight: The mean initial and final body weights of control males were 7.5 and 8.7 kg, respectively. The mean initial and final body weights of control females were 6.8 and 7.5 kg, respectively. No treatment-related effect on body weight was observed in any group.

4. Food Consumption: No treatment-related effects were observed in any group.

5. Hematology: No treatment-related effects were observed in any group.

6. Blood Chemistry: No treatment-related effects were observed in any group.

7. Organ Weights: No treatment-related effects were observed in any group.

8. Gross Pathology: There were no macroscopic findings related to treatment in any group.

9. Histopathology: There were no microscopic findings related to treatment with porcine or human secretin.

There were no significant adverse effects of synthetic porcine secretin or human secretin at 1.5 or 5 μg/kg dose levels in dogs. The NOEL for sPS or human secretin in dogs appeared to be 1.5-5.0 μg/kg/day and no organ of toxicity could be identified because of the lack of adverse effects at these dose levels.

LABELING: The draft labeling of synthetic porcine secretin conforms to the format specified under CFR 21, subpart B, 201.5 to 201.57 dated April, 1998. However, the following changes should be made in the proposed labeling:

Proposed Labeling:

1. **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Sponsor's Version:

Reviewer's Comments:

Long-term studies are used to evaluate the carcinogenic potential of the test material. However, mutagenic potentials of a test material are not evaluated by long-term studies. Similarly, long-term studies are not used to evaluate the effects of the test compound on fertility.

Therefore the above stated changes should be incorporated in the proposed labeling as recommended below.

Recommendation: The proposed text of sponsor should be modified as stated below:

Carcinogenesis, Mutagenesis, Impairment of Fertility: "Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ———————secretin. Studies to evaluate the possible impairment of fertility or mutagenic potential of ——————— have not been performed."

2. **Pregnancy Category C:**

Sponsor's Version:

PREGNANCY CATEGORY C: Animal reproduction studies have not been conducted with ——— secretin. It is also not known whether ——— secretin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. ——— secretin should be given to a pregnant woman ——— only if clearly needed. ———

Reviewer's Comments: The last sentence in the above version is unnecessary and should be deleted. Part of the sentence ——— before the last sentence is also unnecessary and should be deleted.

Therefore the above stated changes should be incorporated in the proposed labeling as recommended below.

Recommendation: The proposed text of sponsor should be modified as stated below:

Pregnancy Category C: "Animal reproduction studies have not been conducted with ——— secretin. It is also not known whether ———secretin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ——— secretin should be given to a pregnant woman only if clearly needed."

3. **Nursing Mothers:**

Sponsor's Version:

NURSING MOTHERS: It is not known whether synthetic porcine secretin is excreted in human milk. Because many drugs are excreted in human milk, caution is advised when ——— secretin is administered to a nursing woman. ———

Reviewer's Comments: The last sentence in the above version is unnecessary and should be deleted.

Therefore the above stated changes should be incorporated in the proposed labeling as recommended below.

Recommendation: The proposed text of sponsor should be modified as stated below:

Nursing Mothers: "It is not known whether [redacted] secretin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when [redacted] secretin is administered to a nursing woman."

4. **Overdosage:**

There is no overdosage section in the sponsor's draft label.

Reviewer's Comments: This section should be incorporated in the sponsor's labeling.

Therefore the above stated changes should be incorporated in the proposed labeling as recommended below.

Recommendation: The following text should be incorporated in the sponsor's labeling:

Overdosage: "Single intravenous dose of 20 μg/kg of [redacted] secretin was not lethal to mice or rabbits".

SUMMARY AND EVALUATION:

Secretin is a gastrointestinal peptide (27 amino acid) hormone secreted from duodenum when the pH of the duodenal content is less than 4.5. The physiologic function of secretin is to stimulate the exocrine pancreas gland to secrete pancreatic juice containing high amount of bicarbonate and water. In this way, it flushes out pancreatic digestive enzymes into the duodenum and causes alkalization of the duodenum content and provides optimal chemical environment (in terms of pH) for the biological activity of pancreatic enzymes (pancreatic amylase, proteolytic and lipolytic). Biologically derived porcine secretin was approved by FDA in 1981 and marketed since 1981 first by KABI and then since 1989 by Ferring as a diagnostic agent for the following conditions: evaluation of the exocrine pancreatic function and specifically for the diagnosis of chronic pancreatitis, facilitation of collecting desquamated pancreatic duct cells to diagnose pancreatic cancer by cytopathology and for the diagnosis of gastrinoma (Zollinger-Ellison Syndrome) in terms of the stimulation of serum gastrin levels. The dose ranges from 1-2 Clinical Units (3000 CU/mg peptide).

The sponsor has developed synthetic porcine secretin (sPS, 36742, batch 698; lot 03672) with equivalent biological activity [redacted] to the biologically derived secretin (Ferring Secretin 75 clinical units/vial, lot YB4584) as determined by cat bioassay of sPS. The amino acid sequence and structure of synthetic product is identical to that of approved product. The synthetic product claimed to have no potential for transmitting animal pathogen and well characterized by a validated assay method (HPLC). This product will be available in ample quantities and will be more consistent in terms of safety and consistency compared to biologically derived product.

The sponsor in the present New Drug Application, proposed to use Synthetic Porcine Secretin (sPS) in the diagnosis of pancreatic dysfunction (at 0.2 μg/kg by intravenous injection over 1 minute), [redacted], in suspected gastrinoma (Zollinger-Ellison Syndrome at 0.4 μg/kg by intravenous injection over 1 minute) and for the facilitation of [redacted] during ERCP (at 0.2 μg/kg by intravenous injection over 1 minute).

In support of the application, sponsor submitted literature evidences regarding pharmacology and the usefulness of biologically derived secretin as a preferred diagnostic agent in pancreatic dysfunction, biological assay of synthetic porcine secretin, acute intravenous toxicity studies with sPS in mice and rabbits and 14-day intravenous toxicity study with sPS and human secretin in rats and dogs.

The bioassay of synthetic porcine secretin (sPS) was done by using one domestic short hair male cat. Synthetic porcine secretin 36742 (batch 698, lot 03672) was found to be [redacted] biologically active compared to Ferring Secretin (Lot YB 4584) and 1 μg of sPS was found to be equivalent to [redacted] clinical unit (CU) based on the results of the bioassay.

In acute toxicity studies with mice and rabbits, the animals were administered with 20 μg/kg of sPS by i.v. injection. No mortality or clinical signs of toxicity was observed. There was no sign of significant gross pathological changes in either species. However, there was no evidence of compliance with GLP.

In 14-day intravenous toxicity study in rats, animals were treated with 0.4 and 10 μg/kg/day of sPS and human secretin by i.v. bolus injection. No treatment-related clinical signs or mortality was observed. Body weight, food consumption, hematology and serum chemistry parameters were comparable to control. There was no significant change in organ weight and gross or histopathology. The NOEL appeared to be 10 μg/kg/day and no organ of toxicity could be identified because of the lack of any adverse toxicity at the tested doses.

In 2-week intravenous subacute toxicity study in dogs, sPS and human secretin were administered at the doses of 1.5 and 5 μg/kg/day by i.v. bolus injection. There was no mortality or treatment-related clinical signs at any doses. Body weight, food consumption, hematology and serum chemistry parameters were found to be normal. No treatment-related changes were observed in the organ weight, gross or histopathology. The NOEL for sPS in dogs appeared to be 1.5-5 μg/ kg/day and the target organ of toxicity could not be identified because of the lack of any treatment-related toxicity.

The ICH Guidelines for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals dated July 16, 1997 is applicable to chemically synthesized peptides. According to the guidelines, for biopharmaceuticals intended for short-term use (e.g., ≤ to 7 days), repeated dose studies up to two weeks duration in a rodent and non-rodent species (route of administration should be as close as possible to that proposed for clinical use) have been considered adequate to support clinical studies as well as marketing authorization. This submission contains adequate studies for the preclinical safety evaluation of sPS. The ICH guidelines also states that routine genotoxicity studies and standard carcinogenicity bioassays are not applicable to biotechnology-derived pharmaceuticals. This submission meets the guidelines and satisfies the criteria for marketing authorization of synthetic porcine secretin and appears to be safe for the proposed use.

The labeling of synthetic porcine secretin conforms to the format specified under CFR 21, Subpart B, 201.50-201.57 dated April, 1998. However, the suggested changes described in the text, should be incorporated.

RECOMMENDATIONS:

1. From a preclinical standpoint, this NDA may be approved.

2. Sponsor should be asked to change the proposed label of Synthetic Porcine Secretin as suggested in the text of the review.

[/S/]
Tamal K. Chakraborti, Ph.D.

9/10/99
Date

cc:
Original NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakraborti
HFD-180/Dr. Choudary
HFD-345/Dr. Viswanathan

[/S/] 9/16/99

R/D Init.: J. Choudary 8/12/99

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APPEARS THIS WAY
ON ORIGINAL

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NOV - 5 1999

NDA 21,209 **Review # 1**

Sponsor & Address: ChiRhoClin, Inc.
Silver Spring, MD

Date of Submission: October 15, 1999

Date of HFD-180 Receipt: October 28, 1999

Date of Review: November 5, 1999

Product Name: Synthetic Porcine Secretin

Generic Name: ---

Dosage Form: Injection

Pharmacologic Category: Diagnostic

Composition: ---

Indications: For the diagnosis of gastrinoma

Related NDAs: NDA 21,136

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Summary

SUMMARY AND EVALUATION:

This NDA provides for filing over protest for the indication of diagnosis of gastrinoma. The submission does not contain any new pharmacology information. Pharmacology/toxicology data for this preparation was previously reviewed under NDA 21,136.

/S/

Jasti B. Choudary, B.V.Sc., Ph.D.

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary

JBC/hw/11/5/99
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APPEARS THIS WAY
ON ORIGINAL

NDA 21-136
NDA 21-209

This section is Not Applicable

/S/ 3.27.02

Alice Kacuba, Regulatory Health Project Manager, HFD-180

APPEARS THIS WAY
ON ORIGINAL