CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-256

Pharmacology Review(s)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 19, 2004

FROM: Supervisory Pharmacologist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 21,256 (Synthetic Human Secretin/ — Amendments Dated September 15, 2003 and October 10, 2003- Sponsor's Updated Labeling

TO: NDA 21,256

The above cited amendments contain sponsor's updated version of labeling for synthetic human secretin. The following comments and recommendations address the preclinical portions of the labeling.

1) PRECAUTIONS

a) Carcinogenesis, Mutagenesis, Impairment of Fertility:

Comment

This portion of the labeling contains —
— These studies do not contain any information pertinent to this subsection and therefore the statement should be deleted.

Recommended Final Version

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

b) Pregnancy, Teratogenic Effects, Pregnancy Category C:

Comment

In the interest of consistency, synthetic human secretin should be used in place of —

Recommended Final Version

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

c) Nursing Mothers:

Comment

Sponsor's version refers to excretion of secretin in human milk. This should be changed to synthetic human secretin. The wording of the subsection also needs to be changed to achieve concordance with the recommended version in 21 CFR.

Recommended Final Version

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

2) OVERDOSAGE

Comment

The title of this section should be changed from OVERDOSE to OVERDOSAGE. The word — should be changed to synthetic human secretin.

Recommended Final Version

"OVERDOSAGE
A single intravenous dose of synthetic human secretin at 20 mcg/kg was not lethal to mice or rabbits.

/S/

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

cc:
NDA
HFD-180
HFD-181/CSO

HFD-180/Dr. Choudary
HFD-180/Dr. Korvick
HFD-180/Dr. Justice

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/s/

Jasti Choudary
1/19/04 04:18:47 PM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 6, 2001

FROM: Tamal K. Chakraborti, Ph.D.
Pharmacologist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Response to The Comments by Dr. A. Jacobs (dated December 6, 2001) on Pharmacology Review of NDA 21-256 dated November 8, 2001

TO: NDA 21-256

The following addresses Dr. A. Jacobs's comments:

A.

1. Chemical equivalence: Although in the "Executive Summary" section it has not been pointed out, on page 6 under "Detailed Conclusions and Recommendations", the chemical difference between human and porcine secretin has been identified and it is reproduced below:

"The sponsor has developed synthetic human secretin with equivalent biological activity to the biologically derived secretin (Ferring Secretin) as determined by cat bioassay of synthetic porcine secretin (sPS). Porcine and human secretin consist of 27 amino acids with the two forms differing from each other at only two amino acid positions. Human secretin has Glu (glutamic acid) at position 15 and Gly (glycine) at position 16, whereas porcine secretin has Asp (aspartic acid) and Ser (serine), respectively, at these positions."

2.

- ICH Guidelines: ICH Guidelines for the S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals dated July 16, 1997 clearly states that the principles outlined in this guidance may also be applicable to chemically synthesized peptides.

- Impurities: In the Pharmacology portion of the NDA submission, — — were identified in the drug substance at an acceptable level —. These — impurities are qualified according to the "ICH; Guidance on Impurities: Residual Solvents", December 24, 1997. The amount of potential exposures for — (Class 2) and — (Class 2) are —

µg/day, respectively, from maximum dose of synthetic human secretin (20 µg/day). This exposure is way below the permitted daily exposure (PDE) values for [redacted] mg/day) and [redacted] as specified in the above document.

B.

1. The wide pH range (3-6.5) of the reconstituted drug product is probably because of the absence of any buffering system in the drug product.

2. The biological assay for potency on synthetic human secretin has been conducted using a cat bioassay, where the amount of bicarbonate in the pancreatic juice was determined by titration. This has been discussed in pages 1, 14, and 15 of the NDA 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:
NDA
HFD-180
HFD-181/CSO
HFD-540/Dr. Jacobs
HFD-103/Dr. Houn
HFD-103/Ms. Collier
HFD-180/Dr. Choudary
HFD-180/Dr. Chakraborti

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/s/

Tamal Chakraborti
12/6/01 05:19:01 PM
PHARMACOLOGIST

Jasti Choudary
12/6/01 05:23:16 PM
PHARMACOLOGIST

Comments on NDA 21-256 human secretin (synthetic) — 12/6/01
From A. Jacobs

A. My comments at this date pertain to the pharm/tox review but not the labeling.

1. Executive summary:
Under pharmacologic activity: It's not clear that human and porcine secretin would be considered to be "chemically" equivalent, since they differ in sequence, and impurity profiles may differ.

2. p. 7. The paragraph on ICH biotechnology products. This guideline applies to biotechnology products. The statement that this guideline is applicable to chemically synthesized peptides could perhaps be modified. Nowhere in the guideline does it say that this guideline is applicable to chemically synthesized material . Some aspects of the guideline may be relevant to synthesized materials and other aspects may not be. Although human secretin may be similar to porcine secretin in efficacy, the impurity profile could be different. Administration of a drug for one time does not obviate the need for genotox studies. A material that was totally endogeneous would not need genotox studies. However, synthetic impurities could have a genotox potential. The reviewer could decide to waive the need for genotox studies after evaluation of the amount and nature of the impurities. A statement about the pharm/tox evaluation of the impurities would be helpful.

B. Other:

1. Why is the pH range of reconstituted material so large (pH 3-6.5)?

2. Is there a biologic potency assay as part of the specifications for secretin?

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/s/

Abby Jacobs
12/6/01 07:08:28 AM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21, 256

Review number: 1

Sequence number/date/type of submission: 000/March 16, 2000/Original

000/June 14, 2001/Resubmission

Information to sponsor: Yes (x) No ( )

Sponsor: ChiRhoClin, Inc.

Manufacturer for drug substance:

1. /
2. /
3. / (manufacturer of the drug product)

Reviewer name: Tamal K. Chakraborti, Ph.D.

Division name: Gastrointestinal and Coagulation Drug Products (DGCDP)

HFD #: 180

Review completion date: November 8, 2001

Drug:

Trade name: / (Sterile Lyophilized Powder 16 µg Intravenous Injection).

Generic name (list alphabetically): Synthetic Human Secretin

Code name: None

Chemical name: H-His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Glu-Gly-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

CAS registry number: Not available

Mole file number: Not available

Molecular formula/molecular weight: $C_{130}H_{220}N_{44}O_{39}$/3039.44

Relevant INDs/NDAs/DMFs:

1. IND 56, 821 (Synthetic Human Secretin, ChiRhoClin, Inc.)
2. IND 54, 196 (Synthetic Porcine Secretin, ChiRhoClin, Inc.)
3. NDA 21-136 (Synthetic Porcine Secretin, ChiRhoClin, Inc.)
4. NDA 21-209 (Synthetic Porcine Secretin, ChiRhoClin, Inc.)
5. DMF[redacted]

Drug class: Diagnostic

Indication: Synthetic human secretin is indicated for the diagnostic use in exocrine pancreas dysfunction, e.g. chronic pancreatitis, in suspected gastrinoma.

Clinical formulation: Synthetic human secretin is supplied as a lyophilized sterile powder in 10ml vials. Each 10ml vial contains: 16 µg Synthetic human secretin (free powder base), 1.5 mg L-Cysteine hydrochloride monohydrate, and 20 mg Mannitol USP. When reconstituted in 8.0 ml 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.

Route of administration: Intravenous

Proposed use: Same as indication.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: From a preclinical standpoint, this NDA may be approved.

B. Recommendation for Nonclinical Studies: None.

C. Recommendations on Labeling: Sponsor should be asked to change the proposed label of Synthetic Human Secretin as suggested in the text of the review.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: In acute toxicity studies in mice and rabbits, synthetic human secretin was found to be nonlethal at 20 µg/kg. In subacute i.v. toxicity studies in rats and dogs, the NOEL appeared to be 10 and 5 µg/kg/day, respectively. The tested doses did not allow the identification of any target organ of toxicity. Synthetic human secretin showed no relevant toxicity in rats and dogs.

B. Pharmacologic Activity: The pharmacological properties of secretin were well characterized and evidenced in several scientific publications. Pure synthetic human secretin has been demonstrated to be biologically and chemically equivalent to the approved product (Ferring porcine secretin).

C. Nonclinical Safety Issues Relevant to Clinical Use: None.

III. Administrative

A. Reviewer signature: /S/

B. Supervisor signature: Concurrence - /S/

Non-Concurrence - /S/
(see memo attached)

C. cc: list:

Original NDA
HFD-180
HFD-181/CSO

HFD-180/Dr. Chakraborti
HFD-180/Dr. Choudary
HFD-045/Dr. Viswanathan

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

The sponsor has cross-referred NDA 21, 136 for pharmacology/toxicology section of this submission. Pharmacological activities of secretin were reviewed previously under NDA 21, 136 and the pharmacology/toxicology review of NDA 21, 136 is attached in Appendix-I. The sponsor has submitted the bioassay of synthetic human secretin, which was reviewed here.

Biological Assay for Potency on Synthetic Human Secretin

The bioassay of synthetic human secretin was conducted by using one domestic short hair male cat. The biological activities of different batches of synthetic human secretin varied from — — 5% when compared to either synthetic porcine secretin or Ferring secretin as reference standards. The subacute toxicity studies in rats and dogs were conducted with the drug product (Lot 83602) manufactured by This drug product was found to have — 5 biological activity when compared to synthetic porcine secretin or sPS (lot 78104, 4.895 CU/μg)

Pharmacology conclusions: Biologically derived secretin (extracted from porcine duodenum) was approved by FDA as a diagnostic agent for evaluation of exocrine pancreas function and for diagnosis of gastrinoma. It has been marketed in the US since 1981 first by KABI and then since 1989 by Ferring. Pharmacological activities of secretin were well characterized in a number of *in vitro* and *in vivo* experiments as reported in several scientific publications. Secretin has been shown to be useful in the diagnosis of pancreatic dysfunction and significant correlation was obtained between function and histology of the exocrine pancreas when examined by secretin test. Secretin was recommended as the provocation test of first choice in the diagnosis of gastrinoma (Zollinger-Ellison Syndrome or ZES). Overall, the published pharmacological activity of secretin supports the first two proposed indications. The sponsor's product offers several advantages over the biologically derived product such as chemical uniformity, purity, less antigenic potential, more consistency and ready availability.

II. SAFETY PHARMACOLOGY: Does not apply

III. PHARMACOKINETICS/TOXICOKINETICS: Does not apply

IV. GENERAL TOXICOLOGY: The acute toxicity studies in mice and rabbits and subacute toxicity studies in rats and dogs were previously reviewed under NDA 21, 136. The reviews of these studies are attached in Appendix-I.

Summary of individual study findings: In acute toxicity studies with mice and rabbits, synthetic human secretin was not found to be lethal at a dose of 20 μg/kg to either mice or rabbit. There were no clinical signs of toxicity. In 14-day intravenous toxicity study in rats, the NOEL appeared to be 10 μg/kg/day and the target organ of toxicity could be not identified because of the lack of any adverse toxicity at the tested doses (0.4 and 10 μg/kg/day). In 14-day intravenous subacute toxicity study in dogs, the NOEL appeared to be 5 μg/kg/day and the target organ of toxicity could not be identified because of the lack of any treatment-related toxicity.

Toxicology summary: In acute toxicity studies in mice and rabbits, synthetic human secretin was found to be nonlethal at 20 μg/kg. In 14-day i.v. toxicity studies in rats and dogs, the NOEL appeared to be 10 and 5 μg/kg/day, respectively. The tested doses did not allow the identification of any target organ of toxicity.

Toxicology conclusions: Synthetic human secretin showed no relevant toxicity up to 10 μg/kg/day in rats and up to 5 μg/kg/day in dogs.

V. GENETIC TOXICOLOGY: Does not apply

VI. CARCINOGENICITY: Does not apply

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY: Does not apply

VIII. SPECIAL TOXICOLOGY STUDIES: Does not apply

Labeling with basis for findings:

The draft labeling of synthetic human 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 synthetic human secretin. Studies to

evaluate the potential for — impairment of fertility or mutagenicity of synthetic human secretin have not been performed."

2. **Pregnancy Category C:**

Sponsor's Version:

PREGNANCY CATEGORY C: Animal reproduction studies have not been conducted with synthetic human secretin. It is also not known whether synthetic human secretin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Synthetic human 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 synthetic human secretin. It is also not known whether synthetic human secretin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Synthetic human 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 human secretin is excreted in human milk. Because many drugs are excreted in human milk, caution is advised when synthetic human 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 synthetic human secretin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when synthetic human 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: "

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: From a preclinical standpoint, this submission meets the guidelines and satisfies the criteria for marketing authorization of synthetic human secretin and appears to be safe for the proposed use.

General Toxicology Issues: 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 (pH = 5.5) 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 human secretin with equivalent biological activity to the biologically derived secretin (Ferring Secretin) as determined by cat bioassay of synthetic porcine secretin (sPS). Porcine and human secretin consist of 27 amino acids with the two forms differing from each other at only two amino acid positions. Human secretin has Glu (glutamic acid) at position 15 and Gly (glycine) at position 16, whereas porcine secretin has Asp (aspartic acid) and Ser (serine), respectively, at these positions. The amino acid sequence and structure of synthetic product is identical to that of human secretin. 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 Human Secretin in the diagnosis of pancreatic dysfunction (at 0.2 µg/kg by intravenous injection over 1 minute), in suspected gastrinoma (at 0.4 µg/kg by intravenous injection over 1 minute) and for the facilitation o during ERCP (at 0.2 µg/kg

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

The bioassay of synthetic human secretin was conducted by using one domestic short hair male cat. The biological activities of different batches of synthetic human secretin varied from

— ó when compared to either synthetic porcine secretin or Ferring secretin as reference standards.

In acute i.v. toxicity studies with mice and rabbits, synthetic human secretin was not found to be lethal at 20 µg/kg to either mice or rabbit. In subacute i.v. toxicity studies in rats and dogs, the NOEL appeared to be 10 and 5 µg/kg/day, respectively. The tested doses did not allow the identification of any target organ of toxicity because of the lack of any observed toxicity at the tested doses. Overall, synthetic human secretin did show any relevant toxicity in rats and dogs. From the preclinical standpoint, there appears to be no safety issues relevant to the clinical use of this product.

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. In addition, the guidelines also states "biopharmaceuticals that are structurally and pharmacologically comparable to a product for which there is wide experience in clinical practice may need less extensive toxicity testing". As synthetic human secretin is comparable to biologically derived secretin (Ferring, which is available in the market since 1981) in terms of chemical structure and biological potency, this submission contains adequate studies for the preclinical safety evaluation of synthetic human secretin. The standard battery of genotoxicity tests are not required in this case, as the drug will be administered only once. This submission meets the guidelines and satisfies the criteria for marketing authorization of synthetic human secretin and appears to be safe for the proposed use.

Recommendations:

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

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

X. APPENDIX/ATTACHMENTS: Appendix-I (Pharmacology/toxicology review of NDA 21, 136)

Addendum to review: None

Other relevant materials (Studies not reviewed, appended consults, etc.): None

Any compliance issues: None

/S/

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

/S/

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

cc: list:
Original NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakraborti
HFD-180/Dr. Choudary
HFD-045/Dr. Viswanathan

R/D Init. by JChoudary 10/30/01

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/s/

Tamal Chakraborti
11/8/01 01:37:49 PM
PHARMACOLOGIST

Jasti Choudary
11/8/01 04:33:04 PM
PHARMACOLOGIST

A Nonclinical Inspection was not performed during review cycle 2.

RB 3/22/04

APPEARS THIS WAY
ON ORIGINAL

A Statistical Review (carcinogenicity) was not necessary for this application.

RB 3/22/04

A CAC/ECAC was not necessary for this application.

3/26/04

APPEARS THIS WAY
ON ORIGINAL