DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-256

7/27/01

ChiRhoClin, Inc.
Attention: Edward D. Purich, Ph.D.
15500 Gallaudet Ave.
Silver Spring, MD 20905-4176

Dear Dr. Purich:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our May 11, 2000 refuse-to-file letter for the following:

Name of Drug Product: synthetic human secretin for injection

Review Priority Classification: Priority (P)

Date of Application: June 14, 2001

Date of Receipt: June 14, 2001

Our Reference Number: NDA 21-256

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 13, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 14, 2001.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

*{See appended electronic signature page}*

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Melodi McNeil
7/27/01 09:43:34 AM

# MEMORANDUM OF INTERNAL MEETING MINUTES

**MEETING DATE:** July 26, 2001
**TIME:** 3:30-4:30 PM
**LOCATION:** Room 6B-45 (PKLN)
**APPLICATION:** NDA 21-256; synthetic human secretin for injection
**TYPE OF MEETING:** Filing/Planning

**MEETING CHAIR:** Dr. L. Talarico, Division Director

**MEETING RECORDER:** Ms. M. McNeil, Regulatory Health Project Manager

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. L. Talarico, Division Director
Dr. J. Korvick, Deputy Division Director
Dr. H. Gallo-Torres, Medical Team Leader
Dr. M. Barreiro, Medical Officer
Ms. M. Ysern, Acting Chemistry Team Leader
Dr. A. Shaw, Chemistry Reviewer
Dr. J. Choudary, Supervisory Pharmacologist
Dr. T. Chakraborti, Pharmacology Reviewer
Ms. M. McNeil, Regulatory Health Project Manager
Ms. J. DuBeau, Chief, Project Management Staff

Division of Pharmaceutical Evaluation II (HFD-870)
Dr. S. Doddapaneni, Biopharmaceutics Team Leader
Dr. T. Chen, Biopharmaceutics Reviewer

Division of Biometrics (HFD-715)
Dr. T. Permutt, Statistical Team Leader
Dr. W. Chen, Statistical Reviewer

Division of New Drug Chemistry II (HFD-820)
Dr. E. Duffy, Director

Division of Microbiology (HFD-805)
Dr. N. Sweeney, Microbiology Reviewer

Division of Scientific Investigations (HFD-46)
Dr. K. Malek, Investigator

**BACKGROUND:** This NDA was originally submitted March 16, 2000. However, the Division refused to file all four of the proposed indications, due to clinical deficiencies. Specifically, the

NDA contained insufficient clinical data for review. (See the May 10, 2000 filing meeting minutes and the May 11, 2000 refuse to file letter for additional information.)

The applicant, ChiRhoClin, Inc., provided a June 14, 2001 resubmission which purports to address the refuse to file deficiencies. The resubmitted NDA proposes the following indications, all of which were also proposed in the original NDA submission:

1. Diagnosis of pancreatic exocrine
2. Diagnosis of gastrinoma (. ; and
3. Facilitation of r papilla during ERCP

Each of these indications has an orphan designation; the filing date for the application is August 13, 2001.

(Note: In addition to the three indications listed above, the original NDA also provided for synthetic human secretin . This fourth indication is not proposed in the June 14, 2001 resubmission.)

**MEETING OBJECTIVES:**

1. To determine whether the application is fileable
2. To identify the Division management lead for the application
3. To determine the review priority classification for the application
4. To establish review timelines
5. To identify any information requests

**DISCUSSION POINTS:**

1. Clinical:
   a. Filing Issues: None
   b. Information Requests: None
   c. Misc:
      i. The NDA contains the following controlled clinical studies:

(1) **CRC 98-2**; a randomized, crossover study of synthetic human secretin (SHS) vs. synthetic porcine secretin (SPS) for the assessment of exocrine pancreas function in patients with a known result from a previous secretin stimulation test with biologically derived porcine secretin (BPS).

(2) **CRC 99-9**; a randomized, controlled, crossover study of BPS vs. SPS vs. SHS for the assessment of exocrine pancreas function in patients with a diagnosis of chronic pancreatitis.

(3) **CRC 99-8**; a randomized, controlled, crossover study of BPS vs. SPS vs. SHS for the diagnosis of gastrinoma.

(4) **CRC 98-4**; initially, an open-label, non-comparative study of the routine clinical use of SHS as a diagnostic agent and to assist in pancreatic duct cannulation. The applicant amended Protocol **CRC 98-4** to be a placebo controlled crossover study of SHS to facilitate cannulation of the minor duct in patients with pancreas divisum during ERCP.

ii. The Medical Team Leader will inform the Project Manager which sites (if any) are to be inspected by the Division of Scientific Investigations.

2. Chemistry, Manufacturing, and Controls:

a. Filing Issues: None

b. Information Requests: The reviewer noted the following deficiencies in the application:

i. The form FDA 356h does not list all referenced DMFs.
ii. One lot of drug substance was made under non cGMP conditions.
iii. The batch of drug substance that will be used in the to be marketed drug product was not used in any of the preclinical or clinical studies.
iv. There are no specifications for impurities in the finished drug product.

A discussion ensued as to whether the application could be refused for filing (a second time) based on these deficiencies. Ultimately, however, the chemistry representatives decided these were review, rather than filing issues. Accordingly, these deficiencies will be conveyed to the applicant in an information request letter.

c. Misc: The chemistry reviewer will submit an EER for this request as soon as possible. He will notify compliance of the Division Goal Date (see below).

3. Preclinical Pharmacology:

   a. Filing Issues: None

   b. Information Requests: None

   c. Misc: The reviewer commented that the table of contents contains multiple inaccuracies. He also noted a few cases where study abstracts do not match the text of the full report.

4. Biopharmaceutics:

   a. Filing Issues: None

   b. Information Request: The biopharm reviewer was not present at the filing meeting, however, the team leader indicated that there were some requests to be conveyed to the sponsor. These will be conveyed to the project manager after today's meeting.

5. Statistics:

   a. Filing Issues: None

   b. Information Request: The applicant did not provide any statistical analyses as SAS datasets. These will be requested from the applicant.

6. Microbiology:

   a. Filing Issues: None

   b. Information Requests: None

7. Administrative:

   a. Filing Issues: None

   b. Information Requests: The applicant has already been asked to provide the following:

      i. A corrected field copy certification;
      ii. Annotated package insert text;
      iii. Accurate section indices;
      iv. The unnanotated text of the package insert in MS Word 97; and
      v. A revalidated comprehensive index.

c. Misc:

i. Synthetic human secretin is a new molecular entity (chemical type 1), therefore, this NDA will be signed off at the Office level.

ii. Given the current lack of an approved product for the diagnosis of gastrinoma, Dr. Talarico said this application would be designated for priority review. Accordingly, the user fee goal date is December 14, 2001. (Note: The team decided it would be too cumbersome to administratively split the gastrinoma indication into its own NDA.)

iii. To allow time for the action package to be assembled and reviewed (at both the Division and Office levels) by the user fee goal date, the review team agreed that all reviews should be finalized by November 14, 2001.

iv. The draft labeling will be consulted to DDMAC for review.

v. OPDRA has already recommended against use of the proposed tradename ——. The firm was informed of this decision in a July 17, 2001 letter.

vi. Dr. Talarico will be the Division's management lead for this application.

vii. This NDA will be discussed at monthly review team meetings.

**CONCLUSIONS:** The application will be filed, and all identified information requests will be conveyed to the applicant.

**Minutes Preparer:** /S/

**Chair Concurrence:** /S/

**cc: Original**
**HFD-180/Div. Files**
**HFD-180/Meeting Minutes files**
**HFD-180/McNeil**
**HFD-180/Talarico**
**HFD-180/Korvic**
**HFD-180/Gallo-Torres**
**HFD-180/Barreiro**
**HFD-180/Zhou**

**HFD-180/Ysern**
**HFD-180/Shaw**
**HFD-820/Duffy**
**HFD-180/Choudary**
**HFD-870/Doddapaneni**
**HFD-870/Chen**
**HFD-870/Roy**
**HFD-715/Permutt**
**HFD-715/Chen**
**HFD-46/Malek**
**HFD-805/Sweeney**
**HFD-40/Kiester**
**HFD-40/Kober**
**HFD-103/Raczkowski**

**Drafted by: mm/August 3, 2001**
**Initialed by: JChoudary 8/6/01**
**LZhou 8/6/01**
**SDoddapaneni 8/7/01**
**AShaw 8/7/01**
**HGallo-Torres 8/8/01**
**LTalarico 8/9/01**
**final: August 9, 2001**

**MEETING MINUTES**

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/s/
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Melodi McNeil
8/9/01 01:20:50 PM

Lilia Talarico
8/9/01 05:02:32 PM

FILING REVIEW

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

**Date:** July 26, 2001

**From:** Arthur B. Shaw, Ph.D., Review Chemist, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**Through:** Liang Zhou, Ph.D., Chemistry Team Leader, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**To:** NDA 21-256

**Subject:** Filing Review of Resubmission of NDA 21-256 for Synthetic Human Secretin

This memo contains a Filing Review for this drug product and recommends refusal to file for this NDA.

1. There are no DMFs listed in the 356H. The same problem was noted in the original submission of this NDA.
2. The applicant states that one lot of drug substance (DS) was made at [redacted] under GMP conditions. In fact, this was not a GMP procedure. The evidence that it was not GMP is that the manufacturing records provided are are not product-specific. [redacted] also failed the GMP inspection for porcine secretin.
3. Another batch of DS was made by [redacted] This is what is proposed for marketing. There have been no preclinical or clinical studies using this lot. At a minimum, a bridging study will be needed. Both [redacted] used the same [redacted] but they used different [redacted] procedures [redacted] were different. They claim sameness in specifications. This will be part of the review assessment.
4. There are no specifications for impurities in the finished product. The applicant states that these will be provided when a new assay is validated.

On summary, this application is not complete froma CMC point of view.

R/D/ init by MYsern/26-Jul-2001
ABS **ABS F/T/26-Jul-2001**
D:\F\21-256 Synthetic Human Secretin Filing Resubmission Comments.doc

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/s/
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Arthur B. Shaw
7/26/01 03:11:02 PM
CHEMIST

Maria Ysern
7/26/01 03:31:37 PM
CHEMIST

7/24/01

**Division of Gastrointestinal & Coagulation Drug Products**

# ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

**Application Number:** NDA 21-256

**Name of Drug:** — (synthetic human secretin) for Injection

**Sponsor:** ChiRhoClin, Inc.

## Material Reviewed

**Type of Submission (i.e., paper, electronic, or combination):** Paper

**Submission Date:** June 14, 2001

**Receipt Date:** June 14, 2001

**Filing Date:** August 13, 2001

**User-fee Goal Date(s):** If priority, December 14, 2001
If standard, April 14, 2002 (primary)
If standard, June 14, 2002 (secondary)

**Proposed Indication:** The NDA currently proposes three indications:

1. Diagnosis of pancreatic exocrine
2. Diagnosis of gastrinoma (
3. Facilitation of papilla during ERCP ; —

(Note: The list of proposed indications is taken from the applicant's draft package insert. Mixed in with the indications listed above are the words — possibly left over from a previous version of the labeling [see below]. The applicant will be asked to clarify the meaning of these words in the context of the currently submitted draft labeling.)

**Other Background Information:** This NDA was originally submitted March 16, 2000. At that time, it proposed four indications--the three listed above and . The Division refused to file all four of the indications in the original NDA submission due to clinical deficiencies.

The applicant provided a June 14, 2001 resubmission which purports to address the refuse to file deficiencies.

The applicant provided the NDA in triplicate. There are 39 archival volumes (though the FDA form 356h incorrectly indicates there are 40 archival volumes.) The archival volumes have been

numbered 1 through 39 (upper right corner of front jacket cover). The technical volumes are not correctly numbered, nor are they all exact duplicates of the corresponding archival volumes.

**Review**

PART I: OVERALL FORMATTING[a,d,e]

| [Note: Items 1,2,3,4, & 5 must be submitted in paper.] | Y | N | COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers) |
|---|---|---|---|
| 1. Cover Letter | X | | Volume 1; the cover letter is not paginated. |
| 2. Form FDA 356h (original signature) | X | | Volume 1; page 1 |
| a. Establishment information | X | | Volume 1; page 3 |
| b. Reference to DMF(s) & Other Applications | X | | Volume 1; page 1 |
| 3. User Fee FDA Form 3397 | X | | Volume 39; page 1 (Section 18) [Applicant claims Orphan exception; no supporting documentation provided.] |
| 4. Patent information & certification | X | | Volume 39; page 1 (Section 14) |
| 5. Debarment certification (Note: Must have a definitive statement) | X | | |
| 6. Field Copy Certification | | X | An incorrect certification was provided. Applicant will be requested to provide correct certification. |
| 7. Financial Disclosure | X | | Volume 39; page 1 (Section 19) |
| | X | | Volume 1; page 6 to 117 (There are also |

| | | | |
|---|---|---|---|
| 8. Comprehensive Index | | | section indices in each trailer volume; these are largely inaccurate. Only the comprehensive index in Volume 1 is generally accurate.) |
| 9. Pagination | X | | The cover letter is not paginated. In addition, the pagination scheme is unclear and inconsistent. For example, some portions of the NDA are paginated continuously, others are not. As noted in item 8 (above) some of the section indices are incorrect as well, which may make navigation among the volumes difficult. |
| 10. Summary Volume | X | | Volume 3 |
| 11. Review Volumes | X | | Some of the review volumes are not identical to the corresponding archival volumes. The applicant has already been asked to correct this. In addition, the review volumes are numbered differently from the archival volumes. |
| 12. Labeling (PI, container, & carton labels) | | | See Below |
| a. unannotated PI | X | | Volume 2; page 1 |
| b. annotated PI | | X | This item will be requested from the applicant. |
| c. immediate container | X | | Volume 2; page 15 |
| d. carton | X | | Volume 2; page 16 |
| e. patient package insert (PPI) | | X | Not Applicable |
| f. foreign labeling (English translation) | | X | Not Applicable |
| 13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic) | X | | Volume 30; page 1 |
| 14. Case Report Forms (paper or | X | | Volume 31; page 1, Volume 33; page 723, |

| | | | |
|---|---|---|---|
| electronic) (for death & dropouts due to adverse events) | | | Volume 35; page 1472, Volume 36; page 1768, Volume 37; page 2069, Volume 37; page 2222, Volume 37; page 2388, Volume 38; page 2389 |

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

| | Y | N | COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers) |
|---|---|---|---|
| 1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits | X | | Volume 3; page 13 |
| 2. Foreign Marketing History | | X | Not Applicable |
| 3. Summary of Each Technical Section | | | See Below |
| a. Chemistry, Manufacturing, & Controls (CMC) | X | | Volume 3; page 15 |
| b. Nonclinical Pharmacology/Toxicology | X | | Volume 3; page 20 (Note that this summary consists of only a one line description of four studies.) |
| c. Human Pharmacokinetic & Bioavailability | X | | Volume 3; page 21 |
| d. Microbiology | X | | Volume 3; page 34 |
| e. Clinical Data & Results of Statistical Analysis | X | | Volume 3; page 35 |
| 4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies | X | | Volume 3; page 256 |
| 5. Summary of Safety | X | | Volume 3; page 246 |
| 6. Summary of Efficacy | X | | Volume 3; page 71 |

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

| | Y | N | COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers) |
|---|---|---|---|
| 1. List of Investigators | X | | Volume 18; page 1 |
| 2. Controlled Clinical Studies | | | See Below |
| a. Table of all studies | | X | The need for this item will be determined at the filing meeting. |
| b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies) | X | | Volume 21; page 936 (Study CRC9801)<br>Volume 22; page 1276 (Study CRC98-2)<br>Volume 22; page 1524 (Study CRC99-8)<br>Volume 23; page 1762 (Study CRC99-9) |
| c. Optional overall summary & evaluation of data from controlled clinical studies | | X | |
| 3. Integrated Summary of Efficacy (ISE) | X | | Volume 26; page 2960 |
| 4. Integrated Summary of Safety (ISS) | X | | Volume 27; page 1 |
| 5. Drug Abuse & Overdosage Information | X | | Volume 27; page 11 |
| 6. Integrated Summary of Benefits & Risks of the Drug | X | | Volume 27; page 12 |
| | | | |

| | | | |
|---|---|---|---|
| 7. Gender/Race/Age Safety & Efficacy Analysis of Studies | | X | The need for this item will be determined at the filing meeting. |

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

| | Y | N | COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers) |
|---|---|---|---|
| 1. Written Documentation Regarding Drug Use in the Pediatric Population | | X | |
| 2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.) | | | See Below |
| a. Proposed unannotated labeling in MS WORD | | X | This item will be requested of the applicant. |
| b. Stability data in SAS data set format (only if paper submission) | | X | The need for this item will be determined at the filing meeting. |
| c. Efficacy data in SAS data set format (only if paper submission) | | X | The need for this item will be determined at the filing meeting. |
| d. Biopharmacological information & study summaries in MS WORD (only if paper submission) | | X | The need for this item will be determined at the filing meeting. |
| e. Animal tumorigenicity study data in SAS data set format (only if paper submission) | | X | Not Applicable |
| 3. Exclusivity Statement (optional) | | X | |

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

**Additional Comments:** The comprehensive index contains some typographical errors. For example, it indicates the Synopsis for Study CRC99-9 can be located in Volume 23, page 1726, however this information is actually located in Volume 23, page 1762.

**Conclusions**

1. The applicant has already been requested to provide replacement review volumes one, two, three, and 39 to address the discontinuity between the review and archival volumes.

2. The applicant will be requested to provide the following:

   a. A corrected field copy certification;
   b. Annotated package insert text;
   c. Accurate section indices; and
   d. The unnanotated text of the package insert in MS Word 97.

3. The applicant will be requested to revalidate the comprehensive index.

4. The need for the following items will be determined at the filing meeting:

   a. Table of all controlled studies;
   b. Subgroup group analyses (age, gender, race);
   c. Stability data in SAS format;
   d. Efficacy data in SAS format; and
   e. Biopharmacology information and study summaries in MS Word.

/S/

Regulatory Health Project Manager

cc:

Original NDA
HFD-180/Div. Files
HFD-180/RPM/
HFD-180/Talarico
HFD-180/
draft: mm/July 3, 2001
r/d Initials: JChoudary 7/5/01
SDoddapaneni 7/9/01
TPermutt 7/9/01
AAl-Hakim 7/9/01
HGallo-Torres 7/12/01
LTalarico 7/12/01
final: July 24, 2001

ADMINISTRATIVE REVIEW

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/s/
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Melodi McNeil
7/24/01 11:41:51 AM
CSO

Lilia Talarico
7/24/01 03:19:44 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-256

**DISCIPLINE REVIEW LETTER**

7/17/01

ChiRhoClin, Inc.
Attention: Edward D. Purich, Ph.D.
15500 Gallaudet Ave
Silver Spring, MD 20905-4176

Dear Dr. Purich:

Please refer to your March 16, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic human secretin for injection.

We also refer to your resubmission dated June 15, 2001, which contained the response to our May 11, 2000 refuse to file letter.

We have completed our review of your proposed proprietary name, ——— and recommend against its use at this time. We refer you to 21 CFR 201.10(c)(5), which states that labeling may be misleading if the spelling or pronunciation of a proprietary name may be confused with the established name of a different drug or ingredient. In this regard we have found — oo similar to Secretin. This similarity was confirmed in three verbal prescription drug studies performed by the Office of Post-Marketing Drug Risk Assessment. Twenty participants (N=31) interpreted — with Secretin.

We acknowledge that your intention in adding the prefix, " — to "secretin" may have been to indicate that this product is a synthetic *human* secretin, and to differentiate this name from other secretin products. However, the —" portion of the name may not be accentuated when the product is ordered verbally, and therefore, not easily heard. We recognize that if more than one secretin product becomes available, prescribers will have to specify human, porcine, synthetic, or non-synthetic secretin. However, unless prescribers specify the type of secretin consistently when ordering the drug, there is the potential for medication errors.

In addition to the proprietary name, there are safety concerns regarding the dosing of the proposed product. Your product is dosed in micrograms and not in clinical units (CU), which was used with Secretin-Ferring. Introducing a different dosing unit may cause confusion for health practitioners who are familiar with clinical units when using Secretin-Ferring.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final

decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

*{See appended electronic signature page}*

/S/

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/
---
Arthur B. Shaw
7/17/01 04:11:02 PM
Signing for Liang Zhou

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-256

**INFORMATION REQUEST LETTER**

7/10/01

ChiRhoClin, Inc.
Attention: Edward D. Purich, Ph.D.
15500 Gallaudet Ave
Silver Spring, MD 20905-4176

Dear Dr. Purich:

Please refer to your March 16, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic human secretin for injection.

We also refer to your resubmission dated June 15, 2001, which contained the response to our May 11, 2000 refuse to file letter.

Based on a preliminary administrative review of the resubmission, we have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please specify how many archival volumes are in the June 15, 2001 resubmission. According to the Form FDA 356h, the resubmission contains 40 archival volumes. However, only 39 archival volumes could be located.

2. Your submitted draft package insert includes the following proposed indications:

   a. Diagnosis of pancreatic exocrine

   b. Diagnosis of gastrinoma ( ), and

   c. Facilitation of papilla during ERCP ;

   However, among this list of indications are the words, possibly left over from a previous version of the labeling. Please clarify exactly which indications are proposed in this application.

3. Please provide the text of the package insert, with annotations in accordance with 21 CFR 314.50(c)(2)(i).

4. Please provide mock-ups of the immediate container and carton labeling, in color if possible.

5. Please provide an electronic copy (MS Word 97) of the unnanotated package insert text.

6. Your User Fee FDA Form 3397 claims an Orphan exception to the user fee requirement, however, no supporting documentation for the Orphan Drug designation was provided. Please provide this information.

7. In accordance with 21 CFR 314.50(l)(3), please provide a certification that the field copy of this application is a true copy of the archival chemistry, manufacturing, and controls technical section. The submitted certification is incorrect.

8. A preliminary review of both the comprehensive index and the individual volume indices has revealed numerous inaccuracies. For example, the comprehensive index indicates that the synopsis for study CRC99-9 can be located in Volume 23, page 1726, however, this information is actually located in Volume 23, page 1762. Please re-validate the comprehensive and individual volume indices and submit corrected versions.

Please provide seven copies of your response to requests listed above. These should be provided as archival (blue), clinical (tan), chemistry, manufacturing, and controls (red), pharmacology (yellow), biopharmaceutics (orange), statistics (green), and microbiology (white) copies.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

*{See appended electronic signature page}*

/S/

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Julieann DuBeau
7/10/01 03:13:45 PM

OCT 13 2000

**CONSULTATION RESPONSE**
**Office of Post-Marketing Drug Risk Assessment**
**(OPDRA; HFD-400)**

| DATE RECEIVED: 6/ 6/ 2000 | DUE DATE: 10/ 5/ 2000 | OPDRA CONSULT #: 00-0177 |
|---|---|---|

**TO:**

Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
(HFD-180)

**THROUGH:**

Brian Strongin
Project Manager
(HFD-180)

**PRODUCT NAME:** —— (synthetic human secretin for injection)

**MANUFACTURER:**
ChiRhoClin, Inc.

**NDA #:** 21-256

**SAFETY EVALUATOR:** Lauren Lee, Pharm.D.

**OPDRA RECOMMENDATION:**

OPDRA does not recommend the use of the proprietary name, —— We recommend that the Division of Gastro-Intestinal and Coagulation Drug Products request the manufacturer to submit a new proprietary name for review.

/S/ 10/11/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 10/13/00

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment**
**HFD-400; Rm. 15B-03**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE REVIEWED:** September 20, 2000

**NDA#:** 21-256

**NAME OF DRUG:** [redacted] (synthetic human secretin for injection)

**NDA HOLDER:** ChiRhoClin, Inc.

## I. INTRODUCTION:

This consult is in response to a June 6, 2000 request, by the Division of Gastrointestinal and Coagulation Drug Products, to review the proposed proprietary drug name, [redacted] regarding potential name confusion with other proprietary/generic drug names. The container labels, the carton labeling, and the package insert were also submitted for review of possible interventions in minimizing medication errors.

PRODUCT INFORMATION

[redacted] is a synthetic human secretin, which is a gastrointestinal peptide hormone. The primary action of secretin is to increase the volume and bicarbonate content of secreted pancreatic juices. According to the package insert for [redacted] synthetic human secretin (sHS) and synthetic porcine secretin (sPS) were found to have equivalent pharmacological activity in terms of stimulating the exocrine pancreas to secrete juice and bicarbonate. [redacted] is indicated for the diagnostic use in pancreatic dysfunction, [redacted] gastrinoma [redacted], and for the facilitation [redacted] during ERCP. The usual dose is 0.2 mcg/kg by intravenous injection over 1 minute for pancreatic function testing and [redacted] For diagnosis of gastrinoma, the usual dose is 0.4 mcg/kg by intravenous injection over 1 minute. [redacted] is supplied as a lyophilized sterile powder in 10 mL vials containing 16 mcg of the unreconstituted product.

## II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound-alike or look-alike [redacted] to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted prescription analysis studies nsisting of written prescription studies and a verbal prescription study, involving health care practitioners hin FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate tential errors in handwriting and verbal communication of the name.

## A. EXPERT PANEL DISCUSSION

An expert panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, —— Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA medication errors prevention staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The panel discussed the following sound-alike/look-alike drug names:

| Product Name | Generic name; strength | Usual dose | Observation |
|---|---|---|---|
| —— | Synthetic human secretin for injection; 16 mcg | Test dose: 0.2 mcg for potential allergic reaction<br>Pancreatic function testing & ——: 0.2 mcg/kg by intravenous injection over 1 minute<br>Diagnosis of gastrinoma: 0.4 mcg/kg by intravenous injection over 1 minute | |
| Herceptin | Trastuzumab for injection ; 440 mg | Initial loading dose: 4 mg/kg as a 90-minute infusion.<br>Weekly maintenance dose: 2 mg/kg administered as a 30-minute infusion if the initial loading dose was well tolerated. | *LA/SA |
| Secretin-Ferring<br>***(Discontinued 7/99 per manufacturer)*** | Porcine secretin for injection; 75 CU | Test dose: 0.1-1 CU<br>Pancreatic function testing & procedure for obtaining desquamated pancreatic cells for cytopathology: 1 CU/kg by intravenous injection over 1 minute.<br>Diagnosis of gastrinoma: 2 CU/kg by intravenous injection over 1 minute. | *LA/SA |
| —— | Synthetic porcine secretin for injection; 16 mcg | Test dose: 0.2 mcg for potential allergic reaction<br>Pancreatic function testing: 0.2 mcg/kg by intravenous injection over 1 minute<br>Diagnosis of gastrinoma: 0.4 mcg/kg by intravenous injection over 1 minute | *LA/SA |

*LA = Look-alike
*SA = Sound-alike

A number of sound-alike and/or look-alike product names were identified in the OPDRA focus group including Herceptin, Secretin-Ferring, and —— *Of these products,* —— was considered by the OPDRA expert panel to be most significant. Since the name, —— is lengthy, *comprised of two words linked by a hyphen*, the panel expressed concerns regarding the possible use of "Secretin" alone in reference to the drug. The consensus was that "Secretin" and "—— " are very similar. *[OPDRA previously reviewed the name, —— in August 2000, and the name was found to be objectionable.]* In regard to Secretin-Ferring, the manufacturer discontinued this product in July 99. As for Herceptin, the panel concluded that this name lacked convincing look-alike and sound-alike nilarity to the proposed name.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

2. DDMAC – no objections

PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

The studies conducted by OPDRA involved 90* health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of —— with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Written prescriptions, consisting of (known/unknown) drug products and a prescription for —— were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, verbal orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving the prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

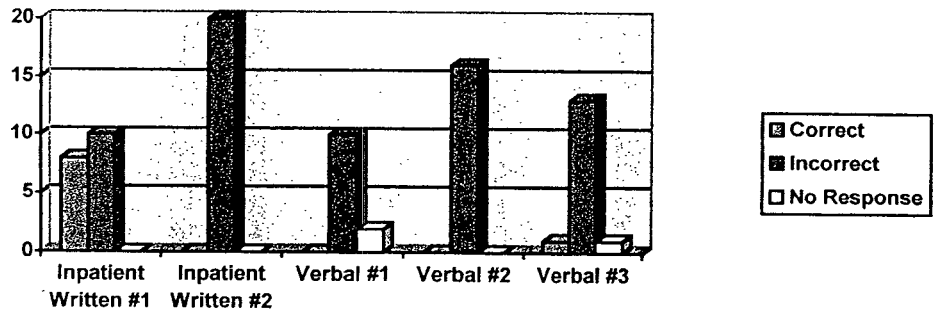
| HANDWRITTEN PRESCRIPTIONS | VERBAL PRESCRIPTIONS |
|---|---|
| *Inpatient #1:* —— 12 mcg IV over 1 minute after baseline duodenal fluids collected. After injection, collect 4 more samples q 15 minutes | *Inpatient #1.* —— 12 mcg IV over 1 minute after baseline duodenal fluids collected. After injection, collect 4 more samples q 15 minutes |
| *Inpatient #2:* —— 12 mcg IV over 1 minute after baseline duodenal fluids collected. After injection, collect 4 more samples q 15 minutes | *Inpatient #2:* —— 12 mcg IV over 1 minute after baseline duodenal fluids collected. After injection, collect 4 more samples q 15 minutes |
| | *Inpatient #3:* —— 12 mcg IV over 1 minute after baseline duodenal fluids collected. After injection, collect 4 more samples q 15 minutes |

*In the first cycle, 90 participants received one of the two written studies or a verbal study#1. After the results were gathered from the first cycle, subsequent two studies, verbal studies #2 & #3, were conducted using some of the same participants from the written studies. More than one verbal study was conducted in order to utilize three different voice samples.

2. Results:

| Study | # of Participants | # of Responses | —— Response | Other Responses | No Response |
|---|---|---|---|---|---|
| Inpatient Written #1 | 31 | 18 (58 %) | 8 (44.4 %) | 10 (55.6 %) | 0 (0 %) |
| Inpatient Written #2 | 30 | 20 (66.7 %) | 0 (0 %) | 20 (100 %) | 0 (0 %) |
| Verbal #1 | 29 | 12 (41.4 %) | 0 (0 %) | 10 (83.3 %) | 2 (16.7 %) |
| Verbal #2 | 31 | 16 (51.6 %) | 0 (0 %) | 16 (100 %) | 0 (0 %) |
| Verbal #3 | 28 | 15 (53.6 %) | 1 (6.7 %) | 13 (86.6 %) | 1 (6.7 %) |
| Total | 149** | 81 (54.4 %) | 9 (11.1%) | 69 (85.2 %) | 3 (3.7 %) |

** This number reflects some of the participants from the written studies who also participated in the verbal studies #2 or #3.



Since —— is a diagnostic agent and would not be dispensed in an outpatient setting, written studies, *which normally consist of inpatient and outpatient prescriptions*, were conducted with only inpatient prescriptions. Both studies consisted of the same drug order, but two different handwriting samples were utilized. The verbal studies were conducted with three different voice samples of the same verbal order.

Among participants in the two written prescription studies, thirty (78.9 %) out of thirty-eight study participants interpreted the name incorrectly. However, most of the incorrect name interpretations were phonetic variations of the proprietary name. According to the *written study #1* results, nine (9) study participants interpreted the name as —— and one (1) participant interpreted the name as ——

In the *written study #2*, twelve (12) study participants interpreted the name as nd six (6) study participants interpreted the name as ). Other interpretations include

Among the three verbal prescription study participants, thirty-nine out of forty-three (90.7 %) participants interpreted the name incorrectly. In the *verbal study #1*, two (2) study participants interpreted the name as . Other interpretations include and —— In addition, two participants did not provide a name response.

However, in the *verbal studies #2 & #3*, twenty (20) study participants interpreted the name as Other interpretations include ——
One of the participants commented that the proposed name, —— could be interpreted as ' —— ' to indicate that a secretin order is written for a female patient.

SAFETY EVALUATOR RISK ASSESSMENT

reviewing the proprietary name, —— the expert panel identified Herceptin, Secretin-Ferring, and —— as possible sound-alike and/or look-alike product names. However, since Secretin-Ferring has been discontinued and is not currently available, the risk of confusion with the proposed name is not significant. As for —— OPDRA previously reviewed this name and did not recommend its use. ——

In regard to Herceptin, : —— Both of these drugs are injectable products that are dosed based on the weights of patients. Also, the numerical doses are similar between —— (0.2 mcg/kg or 0.4 mcg/kg) and Herceptin (2 mg/kg or 4 mg/kg). Moreover, these two drugs are also supplied as lyophilized powder and need to be reconstituted. These two drugs are also prescribed in special patient populations due to their specific indications. However, despite these similarities, these two drugs are different in that —— is given over 1 minute without further dilution during a *diagnostic procedure* whereas Herceptin is further diluted in normal saline and is given as an infusion per chemotherapy protocol. Furthermore, —— is given on a one-time basis whereas Herceptin is a weekly injection. Also, —— to be stored in a freezer, and Herceptin is stored in a refrigerator. Given the above differences in dosing, administration, and storage in combination with the lack of convincing look-alike and sound-alike potential, there is insufficient evidence at this time to conclude that the proposed drug name would be confused with Herceptin.

However, the primary concern regarding the proposed name is that —— contains the term, "Secretin", in both the proprietary name and the established name of the product. Although drug regulations do not prohibit the use of the same term for both the established name and the proprietary name, and there is precedence of such practice with *Secretin-Ferring*, it is important to consider the fact that other secretin formulations could become available in the future. For example, the applicant has also submitted the NDA

21-136 for synthetic *porcine* secretin. — In addition to this drug, other secretin products could potentially be available on the market. In that case, it is inevitable that the established names of the various secretin products would be very similar and would all begin with "Secretin". However, it would be necessary to have the proprietary names that are similar to the established names and create further confusion.

For example, it is possible that ' — ' could be interpreted as "Secretin" without the prefix of the name. In fact, twenty (20) study participants from the verbal studies interpreted the proposed name as "Secretin." We recognize that the intention for adding the prefix, ' — ' to "secretin" may have been to indicate that this product is a synthetic *human* secretin, and to differentiate this name from other secretin products. However, depending on how the name is verbally pronounced, the prefix, " — could be less accentuated than the "secretin" portion of the name, and therefore not easily heard. Although we recognize that if more than one secretin product becomes available, prescribers would have to specify human, porcine, synthetic, or non-synthetic secretin. However, unless prescribers specify the type of secretin *consistently each time* when ordering the drug, there is potential for medication errors.

In our prescription studies, 85.2 % of the interpretations were incorrect. We recognize that there are limitations to the predictive value of these studies primarily due to their sample sizes, and that the majority of the incorrect interpretations were misspelled/phonetic variations of the drug name. However, it is noteworthy that in the *written study #2* and the *verbal studies #1 & #2*, none of the participants interpreted the proposed name correctly. Moreover, as stated above, the participants in the verbal studies *actually* interpreted — as *Secretin*.

Given the above findings, the use of the proprietary name, — is not recommended at this time.

addition to the proprietary name, there are safety concerns regarding the dosing of the proposed product. secretin is dosed in micrograms and not in clinical units (CU), which was used in Secretin-Ferring. nough the package insert provides the equivalency between CU and mcg, introducing a new dosing unit may cause confusion for health practitioners who are familiar with Secretin-Ferring.

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton labeling, and the package insert of — OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has identified the following areas of possible improvement, which might minimize potential user error.

### A. CONTAINER LABEL

1. We recommend revising the statement, "Caution: Federal law prohibits dispensing without prescription" to "Rx Only" per FDA Modernization Act of 1997. Revising this statement would also increase available label space.

2. We recommend adding the statement, "For Intravenous Use Only", on the front of the label.

3. We recommend adding the statement, "For Single Use Only", on the front of the label.

### B. CARTON LABELING

1. We recommend revising the statement, "Reconstitute with **8.0 mL** of Sodium Chloride..." to read, "Reconstitute with **8 mL** of Sodium Chloride..." The use of terminal zeros could increase the risk of 10-fold dosing errors. In addition, if space permits, we recommend adding the expression of the

1 pages redacted from this section of the approval package consisted of draft labeling

## IV. RECOMMENDATIONS:

OPDRA does not recommend the use of the proprietary name, ~~[redacted]~~

OPDRA recommends the above labeling revisions that might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam at 301-827-3161.

/S/

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

NDA: 21-256
Office Files
HFD-180; DivFiles; Brian Strongin, Project Manager
HFD-180; Lilia Talarico, Division Director
HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:

HFD-002: Murray Lumpkin, Deputy Center Director for Review Management
HFD-400: Peter Honig, Director, OPDRA
HFD-040: Patricia Staub, Senior Regulatory Review Officer, DDMAC
HFD-440: Mary Dempsey, Project Manager, DDRE II, OPDRA
HFD-400: Sammie Beam, Project Manager, OPDRA

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13 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-256

ChiRhoClin, Incorporated
Attention: Edward Purich, Ph.D.
Chief Executive Officer
15500 Gallaudet Avenue
Silver Spring, MD 20905

JUL 24 2000

Dear Dr. Purich:

Please refer to the meeting between representatives of your firm and FDA on July 6, 2000. The purpose of the meeting was to discuss the refuse-to-file letter.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact me at (301) 827-7310.

Sincerely yours,

/S/

Brian Strongin
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment

# MEMORANDUM OF MEETING MINUTES

**Meeting Date:** July 6, 2000

**Time:** 10:00AM

**Location:** Parklawn Building, 6B-45 Conference Room

**Application:** NDA 21-256; —— (synthetic human secretin)

**Type of Meeting:** Informal Conference Following a Refusal-to-File

**Meeting Chair:** Larry Goldkind, M.D.

**Meeting Recorder:** Brian Strongin

**FDA Attendees, Titles, and Office/Division:**

The Division of Gastrointestinal and Coagulation Drug Products

| | |
|---|---|
| Lilia Talarico, M.D. | Director |
| Steve Aurecchia, M.D. | Deputy Director |
| Larry Goldkind, M.D. | Medical Officer |
| Liang Zhou, Ph.D. | Team Leader, CMC |
| Brian Strongin | Regulatory Health Project Manager |

The Division of Biometrics II

| | |
|---|---|
| Thomas Permutt, Ph.D. | Team Leader, Biometrics |

**External Constituent Attendees and Titles:**

ChiRhoClin, Inc.

| | |
|---|---|
| Seymour Fein, M.D. | Chairman, Medical Director |
| Edward Purich, Ph.D. | CEO |

**Background:**

NDA 21-256, submitted March 16, 2000, provides for the following indications: (1) diagnosis of pancreatic exocrine 2) —— (3) diagnosis of —— and (4) facilitation of —— papilla during ERCP ——

A refusal-to-file letter dated May 11, 2000 characterized the application as not sufficiently complete to merit review, citing a lack of adequate clinical data in the submission related to the use of — All indications were thus refused to file. On May 25, 2000 the firm requested an "informal conference" per 21 CRF 314.101(a)(3) to discuss the refusal to file.

**Meeting Objective:**

To review the Division's decision to refuse-to-file NDA 21-256

**Discussion Points:**

I. The firm's questions were discussed. The questions are italicized below, followed by the Division's responses.

A. *Based on the new, final study report for CRC 99-9 including the new pooled statistical analyses of 98-1 and 98-2 and the initiation of CRC 2000-1, we believe these items enable the synthetic human secretin (sHS) NDA 21-256 to be filed for the diagnosis of exocrine pancreas dysfunction. Does the FDA agree?*

B. *Based on the submission of the CRC 99-8 final study report to NDA 21-256, we believe the sHS NDA 21-256 is fileable for the diagnosis of gastrinoma indication. Does the FDA agree?*

C. *Based on the submission of pivotal data on sPS for the ERCP — indication and the initiation of a similar study for sHS, we believe the sHS NDA 21-256 can be filed for this indication. Does the FDA agree?*

To be considered fileable, an NDA must be sufficiently complete upon submission to permit a substantive review. We advise you to resubmit NDA 21-256 when all pivotal studies, including Study CRC 2000-1, have been completed and final study reports, including all necessary documentation, are available. The following data/information must be submitted for all studies before this application, including all requested indications may be considered fileable:

1. primary data and case report forms for all enrolled subjects;
2. complete study reports including the original protocol, all protocol amendments (if any) and protocols for all combined analyses.

We refer you to the Guideline for The Format and Content of the Clinical and Statistical Sections of New Drug Applications, July 1988, available on the CDER website.

If you request that the application be filed over protest, we will complete our review and take an action based on the data submitted. Alternatively, you may submit separate NDAs for any individual indication for which studies and reports are complete.

I. A discussion of the Division's responses ensued.

The Division reiterated the need for completed and final study reports of all pivotal studies upon submission for an NDA to be considered fileable. The submission of data on a patient-by-patient basis is not acceptable. The firm responded that they have complete study reports for all pivotal studies except CRC 2000-1, which is in progress. They added that their consultants advised them that data from study CRC 2000-1 would not be necessary. Study CRC 2000-1 is a study of pancreatic exocrine response to sHS in normal subjects. The Division responded that data from Study CRC 2000-1 is necessary to establish the ranges of responses in normal volunteers to be distinguished from diseased patients as well as for additional safety data. The sponsor was reminded that complete study reports for Studies CRC 99-9 and 99-8 were not submitted.

The firm asked if it is advisable to reduce the size of CRC 2000-1 from the protocol-specified 30 patients to 12 patients. The Division suggested that they discuss this with their consultant. The adequacy of study size depends, in part, on the range and variability of the results..

The Division requested that safety data for patients with all investigated indications, including autism, be included in the Integrated Summary of Safety. The firm asked if safety data from autism patients should be separated from that from other indications. The Division explained that adverse events related to the patients underlying diagnosis should not be included in the labeling, but that the submission of safety data from patients with all diagnosis should be submitted for the Division's assessment.

The Division reminded the firm that a request to file NDA 21-256 "over protest" must be received by July 30, 2000, sixty days after the request for the "informal conference" was received. In response to the firm's question, the Division explained that it was not necessary to withdraw NDA 21-256 as submitted. The firm could resubmit the additional data and study reports in response to the refusal-to-file letter as suggested. A new user fee due date would be assigned to the application.

Minutes Preparer: /S/

Chair Concurrence: /S/ 12/6.

cc:
Archival NDA 21-256
HFD-180/division file
HFD-180/RPM/B. Strongin
HFD-180/Team Leaders and reviewers

Drafted by: hw/7/21/00
Initialed by: bs/7/21/00
Final: hw/7/24/00
filename: C:\DATA\CSO\N\21256.MEETING.MINUTES.0BS

8/7-24-00

GENERAL CORRESPONDENCE (Minutes Sent)

## MEMORANDUM OF TELECON

DATE: June 15, 2000

APPLICATION NUMBER: NDA 21-256; —— (synthetic human secretin)

BETWEEN:

Name: Ed Purich, Ph.D., CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Chemistry, Manufacturing, and Controls Information Request

### Background

NDA 21-256 for —— (synthetic human secretin), submitted March 16, 2000, provides for the following indications: (1) diagnostic use in pancreatic dysfunction; (2) —— (3) diagnosis of gastrinoma; and, (4) for the facilitation of —— papilla during ERCP ——

### Today's Call

The following information requests were faxed to the firm:

Concerning the chemistry, manufacturing, and controls section of NDA 21-256:

1. Revise the Form FDA 356H (Volume 1.1, page 1) to include a list of Drug Master Files referenced in the application.

2. The letter dated June 28, 1999 from —— —— to you, (Volume 1.3, page 0445) includes responses to an information request letter from the Division concerning your IND for synthetic human secretin. Clarify the IND number and date of the Division's letter. The letter contains information related to various aspects of the identity, strength, synthesis, and purity of the drug substance. Provide these responses directly into the relevant sections of the NDA.

3. Regarding the drug substance, either provide the following or clarify their location in the application:

a. a "full description of the physical and chemical characteristics of the drug substance" [e.g., pI value (isoelectric pH), solubility profile, and solution pH], as specified in the "Guideline For Submitting Supporting Documentation In Drug Applications For The Manufacture Of Drug Substances" (February, 1987);

b. list of all manufacturing and testing sites, including addresses;

c. the source and specifications for all materials used in the synthesis of the drug substance, including specific acceptance specifications for the — (These specifications should be sufficiently detailed as to require no choices of tests or acceptance criteria.);

d. a detailed description of the synthetic procedure, with specific instructions for each step which are sufficiently detailed —

e. a detailed description of the — procedure, with specific instructions for each step which are sufficiently detailed —

f. sample tracings for a typical chromatographic run for each — used in — Provide sample TLC and HPLC analytical chromatograms for the fractions collected across the peak, showing where on the peak the fractions were collected.

4. Regarding the drug product, either provide the following or clarify their location in the application:

a. the names and addresses of all manufacturing and testing facilities for the drug product; and,

b. a list of the finished product specifications, including test methods and acceptance criteria (A "Certificate of Analysis" is not sufficient to fulfill this requirement.).

Provide the requested information in the relevant sections of the submission, rather than in an appendix.

/S/ 6/15/00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-256
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/A.Shaw
HFD-180/L.Zhou

TELECON

STRONGIN 1.1

# MEMORANDUM OF TELECON

DATE: June 12, 2000

APPLICATION NUMBER: NDA 21-256; — (synthetic human secretin)

BETWEEN:

Name: Ed Purich, Ph.D., CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical and Biopharm Information Requests

## Background

NDA 21-256 for — (synthetic human secretin), submitted March 16, 2000, provides for the following indications: (1) diagnostic use in pancreatic dysfunction; (2) —
— (3) diagnosis of gastrinoma; and, (4) for the facilitation of —
— papilla during ERCP —

## Today's Call

The following information requests were faxed to the firm:

1. Clinical:

   A. Provide information on any preclinical toxicology studies using your drug product or any other drug product containing biologic or synthetic porcine secretin or synthetic human secretin.

   B. Provide an integrated summary of safety for the entire database of synthetic human secretin including the current NDA and any IND or NDA studies. Include blood pressure data using pre-dose and post-dose rather than "entry" and "exit" blood pressure values.

II. Clinical Pharmacology and Biopharmaceutics

Submit data to support your claim that the L-cysteine HCL in your formulation —

/S/ 6/12/00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-256
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/H.Gallo-Torres
HFD-180/L.Goldkind
HFD-870/S.Doddapaneni
HFD-870/S.Roy

TELECON

Brian Strongin

APR 27 2000

# MEMORANDUM OF TELECON

DATE: April 20, 2000

APPLICATION NUMBER: NDA 21-256; — (synthetic human secretin)

BETWEEN:

Name: Ed Purich, Ph.D., CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Request Regarding Study CRC 98-2

## Background

NDA 21-256 for — (synthetic human secretin), submitted March 16, 2000, provides for the following indications: (1) diagnostic use in pancreatic dysfunction; (2) — — (3) diagnosis of gastrinoma; and, (4) for the facilitation of — — papilla during ERCP —

## Today's Call

The firm was asked to provide the following items:

1. a financial disclosure form (Form FDA 3455, available on the CDER website);
2. mock-ups of immediate container and carton labeling; and,
3. unannotated labeling on diskette in WORD 97.

The call was then concluded.

/S/ 4/27/00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-256
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/H.Gallo-Torres
HFD-180/L.Goldkind

TELECON

Brian Strongi

# MEMORANDUM OF TELECON

APR 20 2000

DATE: April 20, 2000

APPLICATION NUMBER: NDA 21-256; —— (synthetic human secretin)

BETWEEN:

Name: Ed Purich, Ph.D., CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Request Regarding Study CRC 98-2

## Background

NDA 21-256 for (synthetic human secretin), submitted March 16, 2000, provides for the following indications: (1) diagnostic use in pancreatic dysfunction; (2) —— —— (3) diagnosis of gastrinoma; and, (4) for the facilitation of — — papilla during ERCP — Study CRC 98-2 is entitled "A Randomized, Crossover Study Evaluating Synthetic Porcine Secretin and Synthetic Human Secretin for the Assessment of Exocrine Pancreas Function in Patients with a Diagnosis of Chronic Pancreatitis". Inclusion criteria specify patients with a diagnosis of chronic pancreatitis documented by a prior secretin stimulation test with biologically derived porcine secretin. Case report forms for this study include a notation of the date of the prior secretin stimulation test (SST) and peak bicarbonate measurement, but no other data from the prior SST.

## Today's Call

The firm was asked to provide source documentation for the prior SST result noted in the case report forms. The firm will provide this information. The call was then concluded.

/S/ , 4/20/00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-256
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/H.Gallo-Torres
HFD-180/L.Goldkind

TELECON

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-256

Food and Drug Administration
Rockville MD 20857

ChiRhoClin, Inc.
Attention: Edward Purich, Ph.D.
Chief Executive Officer
15500 Gallaudet Avenue
Silver Spring, MD 20905

MAY 11 2000

Dear Dr. Purich:

Please refer to your March 16, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for — (synthetic human secretin).

We have given your application a preliminary review, and we find it is not sufficiently complete to merit review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. Diagnosis of pancreatic exocrine — This application does not contain completed adequate and well-controlled studies independently documenting the diagnostic value of your product for the diagnosis of pancreatic exocrine insufficiency. As with NDA 21-136, comparative pharmacodynamic and diagnostic data is necessary using an approved diagnostic agent at the comparator. The submitted database contains only three out of twelve planned subjects with such comparative data (Study CRC 99-9). In view of the documented changes in pancreatic function over time in subjects with pancreatitis, comparison to historical secretin stimulation tests using the approved Ferring product cannot be used as comparative data in the current submission. Thus data from Study CRC 98-2 cannot be used in the context of pharmacodynamic compatibility for the diagnosis of pancreatic exocrine disease. A complete study report and data from Study CRC 99-9 as well as comparative data in healthy volunteers must be submitted.

2. —
This application does not contain sufficient clinical data related to the use of your product as
—
Adequate and well-controlled studies showing the diagnostic advantage associated with the use of — in this setting are necessary. The bioassay — cannot be accepted as a surrogate for this proposed indication.

3. Diagnosis of gastrinoma — ): This application does not contain adequate clinical data related to the use of your product for the diagnosis of gastrinoma. Without adequate clinical data from your product used for the diagnosis of gastrinoma, no statements can be made regarding the appropriate dose or sensitivity and specificity of synthetic human secretin.

4. Facilitation of — papilla during ERCP —
— This application does not contain adequate clinical data related to the use of your product to facilitate — papilla during ERCP
— The bioassay for — cannot be accepted as a surrogate for this purposed indication. In addition, there is inadequate medical literature on the safety and efficacy of secretin for use in this proposed indication.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file this application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, this application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

FDA will refund 75% of the user fee submitted with the application. If you decide to file this application over protest, the filing of this application over protest will be regarded by the Agency as a new original application for user fee purposes, and will be assessed a user fee applicable to a new submission.

If you have any questions, call Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely.

/S/

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-256
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Reviewers and Team Leaders
HFD-820/DNDC Division Director
DISTRICT OFFICE

5/5-11-00

Drafted by: BKS/May 5, 2000
Initialed by: LG/May 8, 2000
LT/May 8, 2000
FH/May 11, 2000
final: BKS/May 11, 2000
filename: 21256005.0

REFUSAL TO FILE (RF)

# MEMORANDUM OF 45-DAY PLANNING/FILING MEETING

**Date:** May 4, 2000

**Drug:** —— (synthetic human secretin)

**Attendees:**

| | | |
|---|---|---|
| Lilia Talarico, M.D. | Director | HFD-180 |
| Steven Aurecchia, M.D. | Deputy Director | HFD-180 |
| Hugo Gallo-Torres, M.D., Ph.D. | Medical Team Leader/GI Drugs | HFD-180 |
| Larry Goldkind, M.D. | Medical Officer | HFD-180 |
| Liang Zhou, Ph.D. | Team Leader, CMC | HFD-180 |
| Art Shaw, Ph.D. | Review Chemist | HFD-180 |
| Jasti Choudary, B.V.Sc., Ph.D. | Team Leader, Pharm/Tox | HFD-180 |
| Tamal Chakraborti, Ph.D. | Review Pharmacologist | HFD-180 |
| Tom Permutt, Ph.D. | Team Leader, Biometrics | HFD-715 |
| Milton Fan, Ph.D. | Mathematical Statistician | HFD-715 |
| Suresh Doddapaneni, Ph.D. | Team Leader, Biopharmaceutics | HFD-870 |
| Sandip Roy, Ph.D. | Biopharmaceutics Reviewer | HFD-870 |

**Background:**

NDA 21-256 was submitted and received March 16, 2000. This application provides for the following indications: (1) diagnosis of pancreatic exocrine —— (2) ——, (3) diagnosis of gastrinoma; and, (4) facilitation of —— papilla during ERCP —— The sponsor is ChiRhoClin, Incorporated.

NDA 21-256 is closely related to NDAs 21-136 (submitted 5/14/99, approvable 3/24/00) and 21-209 (submitted 8/17/00, pending). Both applications were submitted by ChiRhoClin, Incorporated and provide for the use of synthetic porcine secretin for the same indications as NDA 21-256. Indications #3 (diagnosis of gastrinoma) and #4 (facilitation of —— from 21-136 were refused to file in July, 1999. The sponsor requested indication #3 be filed over protest. NDA 21-209 was administratively created for this indication because it is a priority indication, and the submission and user fee due dates differ from NDA 21-136.

Efficacy and safety in NDA 21-256 are supported by the following studies:

1. CRC 98-2; a randomized, crossover study of synthetic human secretin (SHS) vs. synthetic porcine secretin (SPS) for the assessment of exocrine pancreas function in patients with a known result from a previous secretin stimulation test with biologically derived porcine secretin (BPS).

2. CRC 99-9; a randomized, controlled, crossover study of BPS vs. SPS vs. SHS for the assessment of exocrine pancreas function in patients with a diagnosis of chronic pancreatitis. The application contained data for only 3 of the planned twelve patients.
3. CRC 99-8; a randomized, controlled, crossover study of BPS vs. SPS vs. SHS for the diagnosis of gastrinoma. The application contained data for only 1 of the planned six patients.
4. CRC 98-4; an open-label, non-comparative study of the routine clinical use of SHS as a diagnostic agent and to assist in pancreatic duct cannulation.

The efficacy studies as well as Study CRC 99-10, a pk/pd study in 12 healthy volunteers, support safety.

**Meeting:**

1. Filing Issues:

   A. Administrative: None

   B. Clinical:

      1. Diagnosis of exocrine pancreas — Dr. Goldkind explained that the application does not contain completed adequate and well-controlled studies for this indication using an approved diagnostic agent as a comparator. Data for only 3 of twelve planned subjects in Study CRC 99-9 has been submitted. He added that, in view of the documented changes in pancreatic function over time in subjects with pancreatitis, comparison to historical secretin stimulation tests using BPS in Study CRC 98-2 cannot be used to evaluate pharmacodynamic comparability of
      2. Dr. Goldkind explained that the application does not contain sufficient clinical data in support of this indication. Adequate and well-controlled studies are necessary.
      3. Diagnosis of Gastrinoma: Dr. Goldkind explained that the application does not contain sufficient clinical data in support of this indication. Without such data, he explained, no labeling statements can be made regarding the appropriate dose or sensitivity or specificity of synthetic human secretin.
      4. Facilitation of papilla during ERCP : Dr. Goldkind explained that the application does not contain adequate, meaningful clinical data in support of this indication. He added that the bioassay for cannot be accepted as a

surrogate for this purposed indication and that there is inadequate medical literature concerning this usage.

C. Pharmacology: None

D. Chemistry/Manufacturing/Controls: None

E. Biopharmaceutics: None

F. Statistics: None

G. Microbiology: None

II. Requests for Information

Information requests regarding the biopharmaceutics, chemistry, manufacturing, and controls, and statistics disciplines will be e-mailed to the Project Manager from the specific reviewers. They will then be forwarded to the firm.

III. Conclusions

It was decided that a refusal-to-file letter would be sent for all indications.

Minutes Preparer: /S/ 5/10/00
Concurrence: /S/ MD 5-10-00

cc:
NDA 21-256
HFD-180/Div.File
HFD-180/Reviewers and Team Leaders

Drafted by: BKS/May 10, 2000
R/d init: LT/May 10, 2000
Final:BKS/May 10, 2000
Filename: Minutes/21256005.0

MEETING MINUTES

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-256

Food and Drug Administration
Rockville MD 20857

ChiRhoClin, Incorporated
Attention: Edward Purich, Ph.D.
Chief Executive Officer
15500 Gallaudet Avenue
Silver Spring, MD 20905

APR 27 2000

Dear Dr. Purich:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: —— (synthetic human secretin)

Therapeutic Classification: Standard (S)

Date of Application: March 16, 2000

Date of Receipt: March 16, 2000

Our Reference Number: NDA 21-256

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 15, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 16, 2001 and the secondary user fee goal date will be March 16, 2001.

Under 21 CFR 314.102© of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

/S/

Brian Strongin
Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-256
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Reviewers and Team Leaders

BS/4-27-00

DISTRICT OFFICE

Drafted by: BKS/April 27, 2000
final: BKS/April 27, 2000
filename: 21256004.0

ACKNOWLEDGMENT (AC)

file decision. At the September 14, 1999 conference, the Division recommended performing additional studies for both indications. The firm agreed, and on October 15, 1999 requested that indication #3 be filed "over protest". NDA 21-209 provides for the diagnosis of gastrinoma. It was administratively created by splitting off this indication from NDA 21-136 because the diagnosis of gastrinoma is a priority indication and because the submission, receipt, and filing dates for NDA 21-209 and NDA 21-136 differ.

**Review**

PART I: OVERALL FORMATTING[a,d,e]

| [Note: Items 1,2,3,4, & 5 must be submitted in paper with original signature.] | Y | N | COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers) |
|---|---|---|---|
| 1. Cover Letter | Y | | Volume 1, unpaginated section of the volume |
| 2. Form FDA 356h | Y | | Volume 1, page 1 |
| a. Reference to DMF(s) & Other Applications | Y | | INDs 54,196; 56,821; — |
| 3. Patent information & certification | Y | | Volume 24, pages 6958 and 6959 |
| 4. Debarment certification (Note: Must have a definitive statement) | Y | | Volume 1, page 0003 |
| 5. Financial Disclosure | | N | This form will be requested from the firm. |
| 6. Comprehensive Index | Y | | The index is placed at the beginning of each volume. |
| 7. Pagination | Y | | Pagination is consecutive and continuous from the first to the last volume. |
| 8. Summary Volume | Y | | Volume 2 |
| 9. Review Volumes | Y | | |
| 10. Labeling (PI, container, & carton labels) | Y | | |
| a. unannotated PI | Y | | FPL: Volume 8, page 1959 |

| | | | |
|---|---|---|---|
| b. annotated PI | Y | | Volume 2, page 15 and Volume 8, page 1914 |
| c. immediate container | | N | Mock-up labeling will be requested. |
| d. carton | | N | Mock-up labeling will be requested. |
| e. foreign labeling (English translation) | | N | N/A |
| 11. Foreign Marketing History | Y | | Volume 2, page 27 |
| 12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic) | Y | | Volume 19 |
| 13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events) | Y | | CRC 99-10: Volume 20, page 5146<br>CRC 98-1: Volume 21, page 5860<br>CRC 98-2: Volume 22, page 6067<br>CRC 99-8: Volume 22, page 6272<br>CRC 99-9: Volume 22, page 6288<br>CRC 98-4: Volume 22, page 6339 |

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

| | Y | N | COMMENTS<br>(If paper: list volume & page numbers)<br>(If electronic: list folder & page numbers) |
|---|---|---|---|
| 1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits | Y | | Volume 2, page 0025 |
| 2. Summary of Each Technical Section | | | |
| a. Chemistry, Manufacturing, & Controls (CMC) | Y | | Volume 2, page 0028 |
| b. Nonclinical Pharmacology/Toxicology | Y | | Volume 2, page 0033 |

| | | | |
|---|---|---|---|
| c. Human Pharmacokinetic & Bioavailability | Y | | Volume 2, page 0038 |
| d. Microbiology | Y | | Volume 2, page 0049 |
| e. Clinical Data & Results of Statistical Analysis | Y | | Volume 2, page 0051 |
| 3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies | Y | | Volume 2, page 0260 |
| 4. Summary of Safety | Y | | ISS only: Volume 17, page 4724 |
| 5. Summary of Efficacy | Y | | ISE only: Volume 16, page 4722 |

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

| | Y | N | COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers) |
|---|---|---|---|
| 1. List of Investigators | Y | | Volume 13, page 1390 |
| 2. Controlled Clinical Studies | Y | | |
| a. Table of all studies | | N | |
| b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies) | Y | | See Attachment |
| c. Optional overall summary & evaluation of data from controlled clinical studies | Y | | ISE only: Volume 16, page 4722 |
| 3. Integrated Summary of Efficacy (ISE) | Y | | Volume 16, page 4722 |
| 4. Integrated Summary of Safety (ISS) | Y | | Volume 17, page 4724 |

| | | | |
|---|---|---|---|
| 5. Drug Abuse & Overdosage Information | Y | | Volume 17, page 4726 |
| 6. Integrated Summary of Benefits & Risks of the Drug | Y | | Volume 17, page 4727 |
| 7. Gender/Race/Age Safety & Efficacy Analysis Studies | | N | We will discuss the need for these analyses at the filing meeting |

Y = Yes (Present), N = No (Absent)

PART IV: MISCELLANEOUS[d,e]

| | Y | N | COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers) |
|---|---|---|---|
| 1. Written Documentation Regarding Drug Use in the Pediatric Population | | N | We will discuss the need for this at the filing meeting. |
| 2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.) | | N | |
| a. Proposed unannotated labeling in MS WORD | | N | This will be requested from the firm. |
| b. Stability data in SAS data set format (only if paper submission) | | N | We will discuss the need for this at the filing meeting. |
| c. Efficacy data in SAS data set format (only if paper submission) | | N | We will discuss the need for this at the filing meeting. |
| d. Biopharmacological information & study summaries in MS WORD (only if paper submission) | | N | We will discuss the need for this at the filing meeting. |
| e. Animal tumorigenicity study data in SAS data set format (only if paper submission) | | N | N/A |

| | | | |
|---|---|---|---|
| 3. User-fee payment receipt | | N | All indications have received Orphan exemptions. User Fee Cover Sheet requested from the firm 4/18/00. |

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

## Conclusions

This application is filiable from an administrative standpoint. Filing issues, information requests, application classification code (i.e., priority or standard), and chemical classification code (i.e., Type 1, 2 etc.) will be discussed at the filing meeting.

The need for the following items will be discussed at the filing meeting:

1. gender, race, and age safety and efficacy studies;
2. written documentation regarding drug use in the pediatric population;
3. stability data in SAS data set format;
4. efficacy data in SAS data set format; and,
5. biopharmacological information and study summaries in WORD 97.

The following items have been requested from the firm:

1. a financial disclosure form;
2. mock-ups of immediate container and carton labeling;
3. unannotated labeling on diskette in WORD 97; and,
4. a signed copy of the User Fee Cover Sheet.

4/27/00

Brian Strongin
Regulatory Project Manager

4/28/00

## ATTACHMENT

| STUDY NUMBER | SYNOPSIS | PROTOCOL | RELATED PUBLICATIONS | LIST OF INVESTIGATORS | CLIN/STAT REPORT |
|---|---|---|---|---|---|
| CRC 98-1 | Volume 13, page 3233 | Volume 13, page 3271 | Volume 16, Page 4447 | Volume 13, Page 3243 | Volume 13, Page 3232 |
| CRC 98-2 | Volume 14, Page 3476 | Volume 14, Page 3515 | Volume 16, Page 4447 | Volume 14, Page 3486 | Volume 14, Page 3475 |
| CRC 99-8 | Volume 14, Page 3725 | Volume 14, Page 3754 | Volume 16, Page 4447 | Volume 14, Page 3733 | Volume 14, Page 3724 |
| CRC 99-9 | Volume 15, Page 3859 | Volume 15, Page 3895 | Volume 16, Page 4447 | Volume 15, Page 3868 | Volume 15, Page 3858 |

cc:

Original NDA
HFD-180/Div. Files
HFD-180/RPM/B.Strongin
HFD-180/Talarico
HFD-180/Reviewers
draft: BKS/April 27, 2000
final: BKS/April 27, 2000

ADMINISTRATIVE REVIEW

Strongin

# MEMORANDUM OF TELECON

DATE: April 20, 2000

APPLICATION NUMBER: NDA 21-256; —— (synthetic human secretin)

BETWEEN:

Name: Ed Purich, Ph.D., CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Statistical Information Request Regarding Study CRC 98-2

## Background

NDA 21-256 for —— (synthetic human secretin), submitted March 16, 2000, provides for the following indications: (1) diagnostic use in pancreatic dysfunction; (2) ——
—— ; (3) diagnosis of gastrinoma; and, (4) for the facilitation of —
— papilla during ERCP in patients —

## Today's Call

The firm was asked to provide the following items:

1. SAS data sets, on diskette, used for the efficacy and safety analyses. Include a text description of each variable on the data diskettes.
2. SAS programs used to perform the statistical efficacy and safety analyses for the data sets requested above. The SAS programs should be able to read data from these data sets and recreate the analyses contained in the NDA.
3. Please verify that the SAS data sets duplicate information submitted to the application.

The call was then concluded.

/S/ 5/11/00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-256
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/H.Gallo-Torres
HFD-180/L.Goldkind

TELECON

**Review of Amendment of Request for Orphan-Drug Designation**

| | |
|---|---|
| Date received: | 02/04/2000 |
| Date assigned: | 02/08/2000 |
| Date completed: | 02/16/2000 |

FILE COPY

| | |
|---|---|
| Designation number: | — |
| Drug name: | Synthetic human secretin |
| Route of administration: | Intravenous injection |
| Trade name: | None |
| Sponsor: | ChiRhoClin, Inc.<br>15500 Gallaudet Ave.<br>Silver Spring, MD 20905 |
| Contact Person: | Edward Purich, PhD<br>Phone #: 301 384-1554 |
| Proposed diagnostic indication: | To facilitate ]<br>during endoscopic<br>retrogradecholangiopancreatography (# — |

COPY 2/4/00

## 1. Background

The sponsor previously submitted two requests for orphan-drug designation of synthetic human secretin for the following indications: (1) to facilitate ]
during endoscopic retrogradecholangiopancreatography (ERCP) [application # —
and (2) —
[application # —

On reviewing the above requests, we have determined that secretin is employed in some ERCP procedures to increase the volume of secreted pancreatic juice, thus facilitating cannulation of the pancreatic duct. However, *based on the same mechanism of action*, secretin can also be used in conjunction with other diagnostic procedures for pancreatic disorders, e.g., magnetic resonance cholangiopancreatography (MRCP), or ultrasonography (US). Therefore, to avoid redundant and potentially overlapping orphan designations, we proposed to the sponsor that the diagnostic drug synthetic human

secretin be designated as an orphan drug for use in conjunction with any diagnostic procedures for pancreatic disorders to increase pancreatic fluid secretion, provided that the total cumulative number of patients to whom secretin is administered during these procedures is below the numeric threshold of 200,000 per year. We sent the following comments to the sponsor:

"We have reviewed your request for orphan-drug designation of synthetic human secretin to facilitate during endoscopic retrograde The rationale for its use is based on its primary action in increasing the pancreatic secretory responses. However, by virtue of the same mode of action, synthetic human secretin can also be used in conjunction with other diagnostic procedures, e.g., magnetic resonance cholangiopancreatography (MRCP) or ultrasonography, for pancreatic disorders. This may lead to multiple orphan-drug designation requests for secretin, each with a specific diagnostic procedure, and may result in redundant and overlapping designations. Consequently, we propose the following:

1. Synthetic human secretin should be designated as an orphan-drug in conjunction with all diagnostic procedures for pancreatic disorders that require its use to increase pancreatic fluid secretion, provided that the total cumulative number of patients to whom secretin is administered during all of these procedures is below the numeric threshold of 200,000 per year.

2. For the purpose of orphan-drug designation, the indication should read as follows: ' Please be advised that this indication is not necessarily the same as the indication(s) in the marketing application(s) for secretin.

To facilitate our action on your application, we request that you provide: (1) a list of all diagnostic procedures for pancreatic disorders currently performed in clinical setting (besides ERCP and MRCP) that may require the adjunct use of secretin, and (2) the estimated number of patients who will receive secretin during these procedures. These can be submitted as supplemental information to Application # —

We note that the same synthetic human secretin has previously received separate orphan-drug designations for: (1) the evaluation of exocrine pancreas function in chronic pancreatitis (Designation # ), (2) (Designation # , and (3) the diagnosis of gastrinoma (Designation # . The exclusive approval for these designations, once the marketing applications have been approved, shall be recognized as distinct and separate from the current designation."

## 2. Review of Amendment

The sponsor concurs with our proposal. In addition, the sponsor provides a list of diagnostic procedures in clinical practice that may require the adjunctive use of secretin. The procedures that have not received orphan drug designations are ERCP, MRCP and ultrasonography. The estimated annual numbers of patients who may require the use of synthetic human secretin during ERCP and MRCP have been previously determined by OOPD to be — respectively. The sponsor states that the estimated annual number of patients undergoing pancreatic ultrasonography is — although not all these cases would require the use of secretin. Therefore, the total target population figure is approximately —

The sponsor also submits a more conservative estimate based on: (1) the prevalence of chronic pancreatitis — patients); (2) the annual incidence of pancreatic cancer — (3) the annual number of patients with pancreas divisum ( — of — ERCP procedures per year, or — undergoing ERCP; and (4), the total number of pancreatic MRCP and US — The total target population figure, in this case, is approximately —. The sponsor also indicates that the actual historic use of secretin in the U.S. is fewer than — patients per year [no supporting source data provided].

*Reviewer's Comment*

*Based on these estimations, the annual target population is at most — patients, which is less than the numerical threshold for the purpose of orphan-drug designation.*

## 3. Evaluation and Recommendation

It is recommended that OOPD take the following actions:

1. Orphan-drug designation be granted to synthetic human secretin for use in conjunction with diagnostic procedures for pancreatic disorders to increase pancreatic fluid secretion under designation application # —

2. Request the sponsor to withdraw designation application number —

/S/

Tan T. Nguyen, MD, PhD
CDR, USPHS
MO/OOPD/FDA/HF-35

Concurrence:

/S/

Date: 2/28/00

Marlene E. Haffner, MD, MPH
RADM, USPHS
Director, Office of Orphan Products Development

cc:

HF-35/Designation file # —
HF-35/Chron File
HF-35/Nguyen

Redacted 4

pages of trade

secret and/or

confidential

commercial

information