CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-256

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-256

ChiRhoClin, Inc.
Attention: Edward D. Purich, Ph.D.
Chief Executive Officer
4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866-6129

Dear Dr. Purich:

Please refer to your new drug application (NDA) dated June 14, 2001, received June 14, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Human Secretin for Injection, a synthetic lyophilized sterile powder.

We acknowledge receipt of your submissions dated November 30, 2001, December 3, 2001, October 10, 2003, December 15, 2003, March 2, 2004, March 15, 2004, March 17, 2004, March 30, 2004, April 6, 2004, and April 7, 2004. The October 10, 2003 submission constituted a complete response to our December 14, 2001 action letter.

This new drug application provides for the use of Human Secretin for Injection for:

1. Stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction,

2. Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma, and

3. Stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP).

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

The final printed labeling (FPL) must be identical to, except for including the revisions indicated, the enclosed labeling (text for the package insert, immediate container and carton labels). These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-256**." Approval of this submission by FDA is not required before the labeling is used.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Ryan Barraco, Consumer Safety Officer, at 301-443-8017.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation of Research

Enclosure

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

/s/

Julie Beitz
4/9/04 09:48:39 AM

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Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-256

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

Dear Dr. Purich:

Please refer to your new drug application (NDA) dated June 14, 2001, received June 14, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (synthetic human secretin for injection).

We acknowledge receipt of your submissions dated July 16, August 10, September 26, November 2, and 20, 2001. We also acknowledge receipt of your submissions dated November 30 and December 3, 2001. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry, Manufacturing, and Controls:

According to the NDA, [redacted] is the manufacturer that will be used to supply the drug substance for the marketed drug product. However, [redacted] is the manufacturer that supplied drug substance for the product used during drug development. This NDA contains insufficient data on drug product manufactured with [redacted] drug substance. Further, the information you provided for drug product manufactured with [redacted] drug substance is not adequate to permit extrapolation to drug product manufactured with [redacted] drug substance. No extrapolation can be made for the following reasons:

1. Only one batch of drug substance has been manufactured at [redacted] and at [redacted] so there is no adequate history of manufacturing to permit extrapolation from one manufacturer to the other.

2. The drug substance manufactured by [redacted] was not manufactured with adequate controls.

3. The manufacturing facilities for both [redacted] drug substances were the subject of "Withhold" recommendations from the FDA Office of Compliance.

4. The formulation and manufacturing procedure for the drug product manufactured with — drug substance were not adequately controlled —

5. The assay for drug product manufactured using — drug substance was not shown to be stability-indicating because it was not shown to be capable of detecting and quantitating impurities.

6. The stability data for drug product manufactured using — drug substance is inadequate to support the proposed expiration date of – months.

In order to correct these deficiencies you must:

1. Develop an adequate formulation and/or manufacturing procedure for the drug product that permits manufacturing —

2. Develop and validate an adequate stability-indicating assay.

3. Manufacture three lots of drug product using drug substance manufactured at — under the new conditions developed in response to comment 1, immediately above.

4. Provide sufficient stability data for three lots of drug product manufactured using — drug substance obtained using the acceptable stability-indicating assay developed in response to comment 2, immediately above, in order to determine an expiration date.

5. Provide a statistical analysis of the stability data —

6. Provide an established name that meets the requirements of 21 CFR 299.4(d).

In addition, respond to the Discipline Review letter dated November 21, 2001. DMF — must also be found adequate.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will also be required before this application may be approved.

Clinical:

This application proposes the following indications: 1) diagnosis of pancreatic exocrine — 2) diagnosis of gastrinoma — and 3) facilitation of — papilla during endoscopic retrograde cholangio-pancreatography — However, the clinical data in the NDA tested performance of the drug product in an already diagnosed population. True test performance in an undiagnosed population remains unknown. Nevertheless, the indications supported by the submitted clinical data are functional: 1) stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic

exocrine dysfunction, 2) stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangio-pancreatography (ERCP), and 3) stimulation of gastrin secretion to aid in the diagnosis of gastrinoma. (Similar wording will be used for the functional claims in the synthetic porcine secretin applications as well.)

Additional clinical, pharmacology/toxicology, or other data may be required for approval, depending on the results of the requested CMC investigations. Further, given the magnitude of these CMC deficiencies, labeling comments will be conveyed once the application is otherwise approvable.

Your proposed tradename, — has been reviewed and found acceptable. Note, however, that the tradename will be re-reviewed once the deficiencies in this action letter have been addressed and approval is imminent.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Florence Houn
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