CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-256

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-256 / N-000-AZ **Stamp Date**: 10/10/03

Trade Name: —

Active Ingredient: Synthetic Human Secretin

Sponsor: ChiRhoClin, Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Response to Approvable Letter and Labeling Revisions

Background

NDA 21-256 for synthetic human secretin (sHS) was submitted to the Agency on 3/16/00 for use in the following indications: 1) diagnosis of pancreatic exocrine 2) — 3) diagnosis of gastrinoma (—), & 4) facilitation — during ERCP. The proposed clinical doses of sHS were 0.2 µg/kg for pancreatic function testing and 0.4 µg/kg for the diagnosis of gastrinoma (— . sHS was proposed for marketing as a 16 µg vial, to be administered by I.V. injection over 1 minute.

The original submission for NDA 21-256 was deemed acceptable from a CPB perspective by the CPB Reviewer (See CPB Review by Sandip Roy, Ph.D., dated 11/19/01). Overall, NDA 21-256 was deemed approvable by the Agency pending a complete response by the sponsor to several CMC and clinical deficiencies (See Agency Approvable letter under attachment 1).

In an amendment to NDA 21-256 (dated 10/10/03), the sponsor provided complete responses to the deficiencies outlined in the Agency Approvable letter, including the following revisions to the formulation and manufacturing procedures; — in the initial formulation was replaced with 0.9% sodium chloride solution and the manufacturing facility for the drug product was changed from — to Bell-More Laboratories (Hampstead, MD).

Reviewer Comments

As sHS is administered via the I.V. route, it is unlikely the introduced changes to the manufacturing facility and proposed formulation will have a clinically significant effect on the rate and extent of exposure.

Reviewer Recommendations

NDA 21-256 (synthetic human secretin) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II), and from the view point of OCPB, the application is **acceptable**.

The sponsor should revise the Clinical Pharmacology-related language in the labeling as follows: (Agency changes shown as underlined and deleted text)

[

]

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

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

/s/

Suliman Alfayoumi
3/5/04 12:58:50 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/5/04 01:01:28 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-256	**Brand Name**	
OCPB Division (I, II, III)	DPEII	**Generic Name**	Synthetic Human Secretin
Medical Division	DGICDP, HFD-180	**Drug Class**	Peptide
OCPB Reviewer	Sandip Roy, Ph.D.	**Indication(s)**	For diagnostic use in exocrine pancreas dysfunction. gastrinoma (and for the facilitation c papilla during ERCP
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	**Dosage Form**	Lyophilized Sterile Powder for Injection
		Dosing Regimen	0.2 µg/kg body weight by IV injection over 1 min 0.4 µg/kg body weight by IV injection over 1 min (diagnosis of gastrinoma)
Date of Submission	6/14/2001	**Route of Administration**	Intravenous
Estimated Due Date of OCPB Review		**Sponsor**	ChiRhoClin, Inc., Silver Spring, MD
PDUFA Due Date	12/14/2001	**Priority Classification**	
Division Due Date	11/19/01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above	**This submision contains data from a single PK study (protocol CRC99-10) that was submitted in support of NDA for Porcine secretin product. The study contains two arms-porcine secretin and human secretin were tested in the respective arms. Therefore, this study was already reviewed as a part of porcine secretin NDA.**			
Primary reviewer Signature and Date	**Sandip K. Roy, 7/26/01**			
Secondary reviewer Signature and Date	**Suresh Doddapanenis, 7/26/01**			

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-256			
Submission(s):	Type:	Suppl.:	Letter Date:	Date Received:
		000	3/16/2000	3/16/2000
		BZ	4/28/2000	4/28/2000
		RS	6/14/2001	6/14/2001
Reviewer:	Sandip K. Roy, Ph.D.			
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180			
Drug:				
Generic Name:	Synthetic Human Secretin			
Other Name(s):	sHS			
Trade Name:	—			
Molecular Weight:	3039.44			
Molecular Formula:	$C_{130}H_{220}N_{44}O_{39}$			
Structural Formula:	His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Glu-Gly-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2			
Relevant IND(s)/NDA(s):	21-209, 21-136 *			
Drug Class:	Peptide			
Dosage Form:	Lyophilized Sterile Powder for Injection			
Route of Administration:	Intravenous			
Dosing Regimen:	0.2 µg/kg body weight by IV injection over 1 min 0.4 µg/kg body weight by IV injection over 1 min (diagnosis of gastrinoma)			
Sponsor:	ChiRhoClin, Inc., Silver Spring, MD			
Proposed Indication:	Diagnosis of pancreatic exocrine Diagnosis of gastrinoma Facilitation o			

*containing identical data.

SYNOPSIS

This NDA is for a SYNTHETIC HUMAN SECRETIN intended for diagnostic use in exocrine pancreas dysfunction, gastrinoma, and for the facilitation o during ERCP. This product received orphan designation for each indication mentioned above. This gastrointestinal peptide hormone was first approved by the FDA in 1981 as biological porcine secretin. ChiRhoClin submitted an NDA earlier for SYNTHETIC PORCINE SECRETIN for the same indications. We recommended approval with a phase IV pharmacokinetic study commitment. The original application had no information on this product. Subsequently, the sponsor submitted the results of this phase IV study, which was deemed adequate by us. This application is still not approved pending several CMC deficiencies.

SYNTHETIC HUMAN and PORCINE SECRETIN differ in the structure by a single amino acid. Since this product is intended for one time diagnostic use, patients are not likely to receive chronic dosing. Thus, only one study was conducted to characterize the pharmacokinetic profile of single, IV dose in normal subjects and this was considered adequate to satisfy the requirement of Human Pharmacokinetics section. This pharmacokinetic data was reviewed earlier because it came from the same study that supported PORCINE SECRETIN product. This was a sequential, uncontrolled, single dose study of the pharmacokinetic profiles of 0.4 µg/kg sPS and sHS given one week apart in 12 normal subjects. After IV bolus administration, plasma concentration of synthetic human secretin rapidly declined to baseline secretin levels within 60 to 90 minutes in most of subjects. The mean AUC observed, which represented sampling to 120 min was nearly 79% of the estimated $AUC_{0-\infty}$. The α-half-life is 3.26 ± 0.28 minutes and the β-half-life was calculated as 45 min. The clearance of synthetic human secretin is 580.9 ± 51.3 mL/minute and the volume of distribution is 2.7 liter.

Recommendation: This NDA is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.

Comment to the sponsor: None

/S/

Sandip K. Roy, Ph.D.
Clinical Pharmacologist

11/14/2001
Date

FT initiated by Suresh Doddapaneni, Ph.D.

c.c. /NDA 21-256
/HFD-180 (Division files, MMcNeil)
/HFD-870 (SDoddapaneni, HMalinowski, SRoy)
/CDR (ZZadeng)

Is the analytical method adequately validated?

A radioimmunoassay method was used which employs rabbit antisera, XAD-2 resin for rapid extraction of secretin from plasma, ^{125}I labeled secretin, and ——— This method is specific for porcine secretin and has been documented in reviews by Chang, T.M and Chey, W.Y. (Dig. Dis Sci. 25: 529-552) and Tia, H.H. and Chey, W.Y. (Anal Biochem. 87: 376-385, 1978). The standard curve in this RIA method included 11 secretin concentrations selected among 1, 2, 3, 5, 7, 10, 20, 30, 50, 70, 100, 200, and 300 pg. The resulting curve had a linear correlation coefficient (R) of 0.98 or greater. Following data was provided based on repeated assay of human plasma sample containing endogenous secretin.

Limit of quantitation:	———
Intra-assay coefficient of variation:	<18%
Inter-assay coefficient of variation:	18%

What pharmacokinetic information about synthetic human secretin was provided under this submission?

Following pharmacokinetic parameters were obtained from a single dose study of 0.4 μg/kg sPS conducted in 12 normal subjects.

Clearance (ml/min)	580.9 ± 51.3
V_d (ml)	2715 ± 2.3
α-$T_{1/2}$ (min)	3.26 ± 0.28
β- $T_{1/2}$ (min)*	45

*Calculate by reviewer

After IV bolus administration, plasma concentration of synthetic human secretin rapidly declined to baseline secretin levels within 60 to 90 minutes in most of subjects. The mean AUC observed, which represented sampling to 120 min was nearly 79% of the estimated $AUC_{0-\infty}$. The α-half-life is 3.26 ± 0.28 minutes and the β-half-life was calculated as 45 min. The clearance of synthetic human secretin is 580.9 ± 51.3 mL/minute and the volume of distribution is 2.7 liter.

Labeling review:

Following labeling changes are recommended in the proposed package insert under "CLINICAL PHARMACOLOGY", "Pharmacokinetics" section.

The entire paragraph should be changed as follows:

[ ]

A. Pharmacokinetics **Report number: CRC99-10**

Study Title **A Single Center Study Evaluating the Pharmacokinetic Profile of Single Intravenous Dose of Synthetic Porcine and Synthetic Human Secretin. Vol. 1.2, p 64. Protocol No. CRC99-10.**

Rationale: The purpose of this study is to characterize the pharmacokinetic profiles of single, IV dose of sPS and sHS products at a dose of 0.4 μg/kg in normal subjects.

Prinicipal Investigator —
—
—

Analytical Facility: —
—

Study Initiation date: November 10, 1999

Objectives

1. To determine the pharmacokinetic profiles of one dose of ChiRhoClin's sPS and one dose of sHS administered intravenously at 0.4 μg/kg
2. To evaluate the effect of sPS and sHS on serum gastrin levels in normal subjects
3. To evaluate the safety and tolerance of sPS and sHS in normal subjects

Study Design A sequential, uncontrolled, single dose study of the pharmacokinetic profiles of 0.4 μg/kg sPS and sHS given one week apart in 12 normal subjects

Subjects Age: 21 – 39 yrs (mean = 29.5 yrs)
Weight: 61.4 – 100.5 kg (mean = 77.2 kg)

Treatments Single intravenous bolus doses of sPS (0.4 μg/kg) and sHS (0.4 μg/kg) over 60 seconds were administered one week apart

Methodology

Blood samples: Collected at 0, 2, 4, 6, 8, 10, 15, 20, 30, and 45 min and 1, 1.25, 1.5, and 2 hrs after dosing with sPS and sHS.

Analytical Methods: A radioimmunoassay method was used which employs rabbit antisera, XAD-2 resin for rapid extraction of secretin from plasma, ^{125}I labeled secretin, — — — ıe precision and accuracy were not tested for this assay. Following data was provided based on repeated assay of human plasma sample containing endogenous secretin.

Limit of quantitation:

Intra-assay coefficient of variation: <18%

Inter-assay coefficient of variation: 18%

Pharmacokinetics: Pharmacokinetic parameters determined are AUC, C_{max}, $t_{1/2}$, Cl, K_{el}, and V_d.

Pharmacodynamics: Serum gastrin concentrations were assessed at baseline and at 2, 4, 10, 15 and 30 min post administration of sPS and sHS.

RESULTS

Clinical

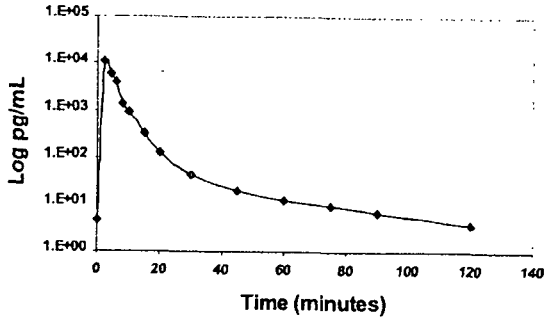
There were no adverse effects reported for sHS. During the treatment period A (sPS), four subjects had 12 adverse effects. These adverse effects included headache, nausea, lightheadedness, numbness and tingling in the left hand, pallor, diaphoresis and hypotension. These adverse effects lasted 10 to 75 min and resolved without specific treatment.

Pharmacokinetics

Synthetic Porcine Secretin:

After IV bolus administration, plasma concentration of porcine secretin concentration rapidly declined to baseline secretin levels within 60 to 90 minutes in most of the subjects. The mean AUC observed, which represented sampling to 120 min was nearly 78% of the estimated $AUC_{0-\infty}$. The α-half-life of porcine secretin is 2.74 ± 0.32 minutes. The β-half-life was calculated as 27.4 min. The clearance of synthetic porcine secretin is 487.2 ± 136.3 mL/minute and the volume of distribution is about 2 liter.

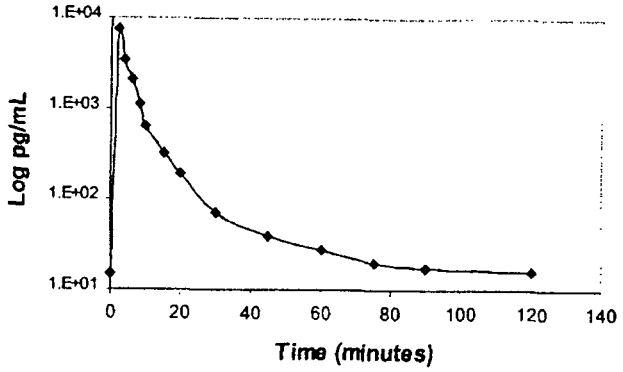
Mean Porcine Secretin Plasma Concentrations



Synthetic Human Secretin:

After IV bolus administration, plasma concentration of synthetic human secretin rapidly declined to baseline secretin levels within 60 to 90 minutes in most of subjects. The mean AUC observed, which represented sampling to 120 min was nearly 79% of the estimated $AUC_{0-\infty}$. The α-half-life is 3.26 ± 0.28 minutes and the β-half-life was calculated as 45 min. The clearance synthetic human secretin is 580.9 ± 51.3 mL/minute and the volume of distribution is 2.7 liter.

Mean Human Secretin Plasma Concentrations



Summary of Pharmacokinetic Parameters for Synthetic Porcine and Human Secretin

Parameters	sPS	sHS

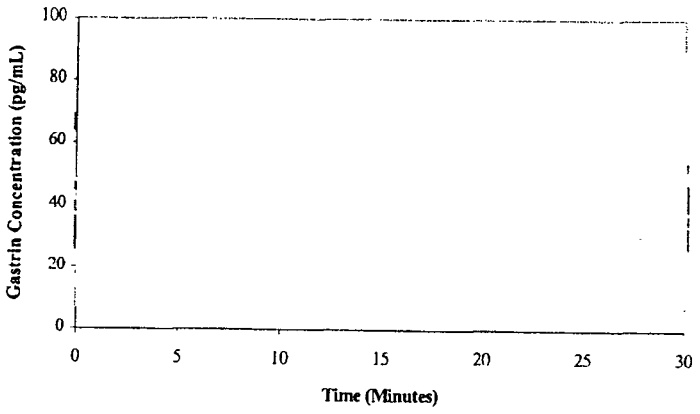
Clearance (ml/min)	487.2 ± 136.3	580.9 ± 51.3
V_d (ml)	1938.2 ± 579.2	2715 ± 2.3
α-$T_{1/2}$ (min)	2.74 ± 0.32	3.26 ± 0.28
β- $T_{1/2}$ (min)*	27.4	45.0

*Calculate by reviewer

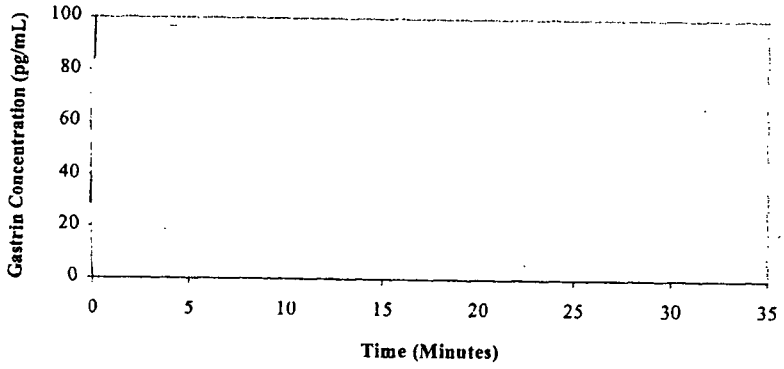
Pharmacodynamics

sPS and sHS had minimal effects on serum gastrin concentrations in normal volunteers. The maximum increase from baseline in an individual was 24 pg/ml (34 to 58 pg/ml at 2 min) for sPS and 32 pg/ml (63 to 95 pg/ml at 4 min) for sHS. A threshold increase of 110 pg/ml is used as the diagnostic paradigm for gastrinoma. Gastrin levels returned to near baseline by 15 min in most subjects and by 30 min in all.

Gastrin Results - sPS



CRC99-10PK for Synthetic Human Secretin Gastrin Results



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/s/

Sandip Roy
11/16/01 03:31:23 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/19/01 01:40:34 PM
BIOPHARMACEUTICS

MAY 25 2000

New Drug Application

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-256			
Submission(s):	Type:	Suppl.:	Letter Date:	Date Received:
		000	3/16/2000	3/16/2000
		BZ	4/28/2000	4/28/2000
Reviewer:	Sandip K. Roy, Ph.D.			
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180			
Drug:				
Generic Name:	Synthetic Human Secretin			
Other Name(s):	sHS			
Trade Name:	—			
Molecular Weight:	3039.44			
Molecular Formula:	$C_{130}H_{220}N_{44}O_{39}$			
Structural Formula:	His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Glu-Gly-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2			
Relevant IND(s)/NDA(s):	21-209, 21-136 *			
Drug Class:	Peptide			
Dosage Form:	Lyophilized Sterile Powder for Injection			
Route of Administration:	Intravenous			
Dosing Regimen:	0.2 µg/kg body weight by IV injection over 1 min 0.4 µg/kg body weight by IV injection over 1 min (diagnosis of gastrinoma)			
Sponsor:	ChiRhoClin, Inc., Silver Spring, MD			
Proposed Indication:	• Diagnosis of pancreatic exocrine • / • Diagnosis of gastrinoma • Facilitation of during ERCP			

*containing identical data.

Items included in NDA (CTD)	**Yes**	**No**	**Request**
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies		X	
Mass Balance Study		X	
BA Studies		X	
Absolute BA		X	
Relative BA		X	
BE Studies		X	
Average BE		X	
Population BE		X	
Individual BE		X	
Food-Drug Interaction		X	
Dissolution Tests (*In Vitro-In Vivo* Comparison Studies)		X	
Studies Using Human Biomaterials		X	
Plasma Protein Binding Studies**	X		
Blood/Plasma Ratio		X	

Metabolism Studies Using Hepatocytes, Microsomes,etc		X	
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies	X		
PK, and Initial Safety and Tolerability in Healthy Volunteers	X		
Single Dose	X		
Multiple Dose		X	
PK, and Initial Safety and Tolerability in Patient Volunteers		X	
Single Dose		X	
Multiple Dose		X	
Dose Proportionality		X	
Single Dose		X	
Multiple Dose		X	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors		X	
Ethnicity		X	
Gender		X	
Pediatrics		X	
Geriatrics		X	
Renal Impairment**	X		
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors		X	
Drug-Drug Interaction: Effects on Primary Drug		X	
Drug-Drug Interaction: Effects of Primary Drug		X	
Population PK studies		X	
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers***	X		
PK/PD studies in patients		X	
Individual Datasets for all PK and PK/PD studies in electronic format		X	
Other		X	
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	

**only literature data provided
***no analysis

Is this application is fileable?

Yes. This report includes analysis of pharmacokinetic study conducted in 12 normal subjects given single intravenous doses of (0.4 μg/kg) of synthetic human secretin (sHS) and synthetic porcine secretin (sPS).

Study Title: A Single Center Study Evaluating the Pharmacokinetic Profile of a Single Intravenous Dose of Synthetic Porcine and Synthetic Human Secretin in Normal Subjects

Analytical Method: Radioimmunoassay (RIA) method was used for quantitating synthetic human secretin in plasma.

Are there any unresolved issues or information that need to be requested from the sponsor?

The sponsor has submitted data for stability data for samples in plasma, since secretin is a peptide hormone which is susceptible to — degradation. The same issue needs to be addressed for NDA 21-256 since both the products are similar. Synthetic Human Secretin like any other secretin is expected —
— As pointed out earlier, this could effect the amount of hormone administered or assayed. Differences in the impurity profiles between bPS and hPS could result — — and this might result in

different dosages. L-cysteine HCl was included in the product formulation — however no data was provided to support this claim.

Recommendation: This NDA is fileable from the Clinical Pharmacology and Biopharmaceutics perspective.

Comment to the sponsor:

You have submitted stability data for samples in plasma considering the susceptibility of secretin to — degradation. However, synthetic human secretin like any other secretin —

This could effect the amount of hormone administered or assayed. You have included L-cysteine HCl in the product formulation, — no data was provided to support this claim.

/S/

Sandip K. Roy, Ph.D.
Clinical Pharmacologist

5/25/2000
Date

/S/ 5/25/00

FT initiated by Suresh Doddapaneni, Ph.D.

c.c. /NDA 21-256
/HFD-180 (Division files, BStrongin)
/HFD-870 (SDoddapaneni, SHuang, SRoy)
/CDR (ZZadeng)

An Abuse Liability Review was not requested during review cycle 2.

RB 3/22/04

See team meeting dated 8/9/01 under "Project Manager" tab where it states that no DSI inspections were needed.

RB 3/25/04

APPEARS THIS WAY
ON ORIGINAL