CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020772

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

MEMORANDUM OF TELECON

DATE: March 24, 1998

APPLICATION NUMBER: NDA 20-772; Sucraid (sacrosidase) Oral Solution

BETWEEN:

Name: Dr. Dayton Reardan, Regulatory Affairs
Phone: Dr. Lowell, Borgen, Project Manager
Representing: Orphan Medical, Inc.

AND

Name: Ms. Melodi McNeil, Project Manager
Dr. Eric Duffy, Chemistry Team Leader
Dr. Art Shaw, Chemistry Reviewer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Dr. John Gibbs, Director
Dr. Steve Koepke, Deputy Director
Division of New Drug Chemistry II

SUBJECT: March 16, 1998 Chemistry IR letter

BACKGROUND: NDA 20-772 was submitted May 6, 1997 by Orphan Medical, Inc. and provides for Sucraid Oral Solution in the treatment of the genetically determined sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID). The application was Approvable (AE) November 6, 1997 pending the resolution of (among other things) chemistry, manufacturing, and controls deficiencies.

The firm responded to the AE letter in a December 12, 1997 amendment. In a March 6, 1998 chemistry review of this amendment, a number of information requests were identified. They were grouped into the following categories: 1) information to be provided as soon as possible, 2) information to be provided post-approval, and 3) information to be addressed in order to establish a manufacturing baseline. These requests were transmitted to the firm by FAX in a letter dated March 16, 1998. According to Drs. Shaw, Duffy, Koepke, and Gibbs, none of the items in the letter are approvability issues.

Today's phone call was initiated to learn the firm's time frame for submitting a response.

TODAY'S PHONE CALL: The firm indicated that they are actively engaged in preparing a response to the letter. They estimated that they would be able to submit the response within the next 7-14 days and added that their response would contain a commitment to provide the requested post-approval information.

Dr. Duffy indicated that inspections of this facility would generally originate from CFSAN but stated the Agency would retain the right to conduct a drug inspection if circumstances warranted. The call was then concluded.

/S/ 3/31/98

Melodi McNeil, Project Manager
Regulatory Health Project Manager

cc: Original NDA 20-772
HFD-180/Div. File
HFD-180/Melodi McNeil, Project Manager
HFD-180/Duffy
HFD-180/Shaw
HFD-820/Koepke
HFD-820/Gibbs
RD Init: EDuffy 3/30/98
Final: March 31, 1998

TELECON

MEMORANDUM OF TELECON

DATE: September 23, 1997

APPLICATION NUMBER: NDA 20-772; Sucraid (sacrosidase) Oral Solution

BETWEEN:

Name: Dr. Dayton Reardan, Regulatory Affairs
Phone: (612) 513-6969
Representing: Orphan Medical, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Information

BACKGROUND: NDA 20-772 was submitted May 6, 1997 and provides for Sucraid Oral Solution in the treatment of the genetically determined sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID).

TODAY'S PHONE CALL: Based on the memo dated September 18, 1997 by Dr. Art Shaw, reviewing chemist, I called the firm and requested information

The firm agreed to provide this information and the call was concluded.

Note: The firm was informed in an October 29, 1997 telephone conversation that this information could be provided as a Phase IV commitment. They agreed to provide written documentation of their acceptance of the commitment.

/S/ 10/29/97

Melodi McNeil, Project Manager
Regulatory Health Project Manager

cc: Original NDA 20-772
HFD-180/Div. File
HFD-180/Melodi McNeil, Project Manager
HFD-180/Shaw
HFD-180/Duffy
HFD-870/Kaus
HFD-870/Chen
HFD-180/Gallo-Torres

TELECON

ORPHAN MEDICAL

October 29, 1997

Lilia Talarico, M.D.
Division of Gastrointestinal & Coagulation Drug Products
Center for Drug Evaluation and Research [HFD-180]
Food and Drug Administration
Division Document Room 6B24
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: NDA 20-772, SUCRAID™ (sacrosidase) ORAL SOLUTION, SUCRAID.

Dear Dr. Talarico:

It was communicated to Orphan Medical by phone on September 23, 1997 and in question I.A.10 of the CMC deficiency letter dated September 25, 1997 that FDA would require

Please do not hesitate to call us should you require any additional information on this commitment.

Sincerely yours,

Dayton Reardan

Dayton Reardan, PhD, RAC
Vice President of Regulatory Affairs
Direct phone (612) 513-6969

cc: Melodi McNeil, [HFD-180] by FAX (301) 443-9285

13911 Ridgedale Drive, Suite 475 • Minnetonka, Minnesota 55305 • 612-513-6900 • Fax: 612-541-9209

802
McNeil

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Melodi McNeil, Project Manager	**Phone:** (301) 443-0483
Date: May 19, 1997	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Sucraid	**NDA/ANDA#** NDA 20-772
Established name, including dosage form: sacrosidase Oral Liquid	
Other trademarks by the same firm for companion products: N/A	
Indications for Use (may be a summary if proposed statement is lengthy): Treatment of confirmed or suspected congenital sucrase-isomaltase deficiency (CSID).	
Initial Comments from the submitter (concerns, observations, etc.): Note: the firm's proposed container labeling is included for your convenience; further information is available upon request.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-772; HFD-180/division file; HFD-180/M.McNeil; HFD-180/Duffy

Rev. December 95

REC'D
JUL 21 1997
HFD-180

APPEARS THIS WAY
ON ORIGINAL

Consult #802 (HFD-180)

SUCRAID sacrosidase oral solution

The following look alike/sound alike conflicts were noted: sucralfate and Sucrettes. However, the Committee felt there was a low potential for mix-up with the conflicting names. There were no misleading aspects found in the proposed proprietary name.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/

7/16/97, Chair
CDER Labeling and Nomenclature Committee

RECD
JUL 22 1997
HFD-180
CENTER FOR DRUG EVALUATION AND RESEARCH

M E M O R A N D U M

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

DATE: September 30, 1997

FROM: Deputy Director and Acting Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Approvable Recommendation for SUCRAID™ (sacrosidase) oral solution, NDA 20-772

TO: Acting Director
Office of Drug Evaluation III

Orphan Medical, Inc. has submitted an NDA for sacrosidase oral solution, an enzyme replacement therapy, for use in the treatment of congenital sucrase-isomaltase deficiency.

Congenital sucrase-isomaltose deficiency (CSID) is a chronic malabsorption disease characterized by an autosomal recessive pattern of inheritance. Marked deficiency of synthesis of endogenous sucrase by the brush border of the small intestine prevents the hydrolysis of sucrose to glucose and fructose. The condition is clinically manifested by severe watery diarrhea and failure to thrive. At present, no enzyme replacement therapy is available for patients with CSID and compliance with a sucrose-free diet is difficult.

The efficacy and safety of yeast-derived sacrosidase as replacement therapy were assessed in two controlled clinical trials (studies S-1 and S-2), and in an uncontrolled, long-term (up to 54 months), open-label trial (study S-3). Study S-3 enrolled 34 patients from studies S-1 and S-2 who wanted to continue sucrasidase replacement therapy.

Study S-1 showed inconsistent results of efficacy of sacrosidase on the GI symptoms associated with CSID. On the contrary, study S-2 clearly demonstrated the effectiveness of sacrosidase in treating patients with CSID while consuming a normal sucrose-containing diet. As indicated by Dr. Hugo Gallo-Torres in the medical review of the NDA, study S-2 showed effectiveness in a dose-response fashion using primary efficacy parameters (fewer total stools and higher proportion of patients having fewer total symptoms). This conclusion was supported by the analysis of secondary efficacy parameters (significantly more formed stools as well as significantly fewer watery stools). Sacrosidase therapy prevented the expected rise in breath H_2 excretion with sucrose challenge in both studies S-1 and S-2 and prevented the development of GI distress and diarrhea under conditions of sucrose load in study S-2. The efficacy and safety of sacrosidase were also supported by study S-3.

Based on the review of the overall evidence, we recommend that sacrosidase (SUCRAID™ oral solution) be approved as replacement therapy for CSID.

Although, as pointed out by the medical reviewer, information considered sometimes critical was missing for some patients, it must be noted that clinical trials performed in the patient population studied (infants, children, adolescents) are difficult to perform. Thus, whereas we agree with the statistician's analyses, we disagree with the statistician's suggestion that another independent study is needed. Since CSID is not a common disorder, the largest trial consisted of only 28 patients. The drug is an orphan drug intended for use in a limited overall patient population.

The Division of Pharmaceutical Evaluation II has granted a waiver of evidence to show *in vivo* bioavailability or bioequivalence based on the fact that the material 1) is an accepted food product, 2) is a protein degraded by proteases to amino acids that are absorbed into the systemic circulation and 3) is acting locally within the intestinal tract.

The evidence at hand indicates that sacrosidase is safe.

/S/

Lilia Talarico, M.D.

cc:
NDA 20-772
HFD-180
HFD-103
HFD-180/HJGallo-Torres
f/t 10/1/97 jgw
MED\N\20772709.0LT

EXCLUSIVITY SUMMARY for NDA # 20-772___ SUPPL # N/A

Trade Name Sucraid **Generic Name** sacrosidase
Applicant Name Orphan Medical, Inc. **HFD-** 180

Approval Date 4/9/98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

____

____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

____

____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

____

APPEARS THIS WAY ON ORIGINAL

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # ______ Drug Name____________

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # ____________ ____________

NDA # ____________ ____________

NDA # ____________ ____________

2. Combination product. NOT APPLICABLE

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # ____________ ____________

NDA # ____________ ____________

NDA # ____________ ____________

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

____
____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: ______________________________
____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: ______________________________
____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # ____________________

Investigation #2, Study # ____________________

Investigation #3, Study # ____________________

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _________ Study #_____________
NDA # _________ Study #_____________
NDA # _________ Study #_____________

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _________ Study #_____________
NDA # _________ Study #_____________
NDA # _________ Study #_____________

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # ________________

Investigation #_, Study # ________________

Investigation #_, Study # ________________

APPEARS THIS WAY ON ORIGINAL

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ____ YES /___/ ! NO /___/ Explain: ____

! ______________

Investigation #2 !

IND # ____ YES /___/ ! NO /___/ Explain: ____

! ______________ !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain ______ ! NO /___/ Explain ________

______________________ ! ______________________

______________________ ! ______________________

APPEARS THIS WAY ON ORIGINAL

Investigation #2

YES /___/ Explain ______	NO /___/ Explain ________

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: ________________________________

/S/

Signature ______________ 2/10/98 Date

Title: Project Manager

/S/

Signature of Division Director ______________ 3-31-98 Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

ORPHAN MEDICAL

SECTION 13

Food and Drug Administration

RE: NDA 20,722

January 30, 1997

PATENT CERTIFICATION/INFORMATION

There is no applicable patent which claims the use, method of using, or method of manufacturing of Sucraid™ (sacrosidase) oral solution for the treatment of patients with congenital sucrase-isomaltase deficiency(CSID), as provided for under this NDA 20,722.

Bert Spilker, Ph.D., M.D.
President

13911 Ridgedale Drive, Suite 475 • Minnetonka, Minnesota 55305 • 612-513-6900 • Fax: 612-541-9209

ORPHAN MEDICAL

SECTION 14

Food and Drug Administration

RE: NDA 20,722

January 30, 1997

PATENT CERTIFICATION/INFORMATION

There is no applicable patent which claims the use, method of using, or method of manufacturing of Sucraid™ (sacrosidase) oral solution for the treatment of patients with congenital sucrase-isomaltase deficiency(CSID), as provided for under this NDA 20,722.

Bert Spilker, Ph.D., M.D.
President

13911 Ridgedale Drive, Suite 475 • Minnetonka, Minnesota 55305 • 612-513-6900 • Fax: 612-541-9209

R:\sucrase\nda\suc14pre.doc

ORPHAN MEDICAL

Food and Drug Administration

RE: NDA 20,722

January 30, 1997

GENERIC DRUG ENFORCEMENT ACT OF 1992 CERTIFICATION

This information is submitted in accordance with Section 306(k)(1) of the Act [21 U.S.C 335a (k)(1)].

I certify that Orphan Medical, Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with this New Drug Application for Sucraid™ (sacrosidase) oral solution.

Bert Spilker, Ph.D., M.D.
President

13911 Ridgedale Drive, Suite 475 • Minnetonka, Minnesota 55305 • 612-513-6900 • Fax: 612-541-9209

R:\sucrase\nda\sucgener.doc

NDA 20-772

Orphan Medical, Inc.
Attention: Dayton Reardan, Ph.D.
13911 Ridgedale Drive
Minnetonka, MN 55305

APR 1 1998

Dear Dr. Reardan:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sucraid (sacrosidase) Oral Solution.

We acknowledge receipt of your submission dated December 12, 1997, regarding, among other things, your phase 4 commitment to study the stability of Sucraid at various pH values, including those likely to be found in the stomach.

We have completed review of your Phase 4 data and conclude that your commitment has been fulfilled.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

4-1-98 4/1/98

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

cc:
Original NDA 20-772
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Duffy
HFD-180/Shaw
HFD-92/DDM-DIAB

Drafted by: mm/March 31, 1998/c:\wpfiles\cso\n\20772803.p4
Initialed by: EDuffy 3/31/98
LTalarico 4/1/98
final: April 1, 1998

GENERAL CORRESPONDENCE (PHASE 4 COMMITMENTS)

NDA 20-772

Orphan Medical, Inc.
Attention: Dayton Reardan, Ph.D.
13911 Ridgedale Drive
Minnetonka, MN 55305

MAR 16 1998

Dear Dr. Reardan:

Please refer to your pending May 6, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sucraid (sacrosidase) Oral Solution.

We also refer to your amendment dated December 12, 1997, which contained, among other things, chemistry, manufacturing, and controls information submitted in response to our November 6, 1997 Approvable letter.

We have completed our review of the chemistry, manufacturing, and controls section of your submission and have the following comments and requests: (All volume and page numbers refer to the December 12, 1997 amendment unless otherwise noted.)

A. Please provide the following information as soon as possible:

1. <u>Regarding the Cleaning and Sanitization of the Drug Substance Manufacturing Equipment</u>:

2. <u>Regarding the Drug Substance Manufacturing Procedure:</u>

3. Regarding the reference standard:

   a. Please specify the volume in each vial of reference standard. Also please specify whether the reference standard after use.

   b. Please specify whether the three bottles of drug product are

   c. Please be advised that the specification of is not acceptable. If the purity is

      Therefore the specification for purity

4. Regarding the specifications for the drug substance:

   a. Based upon the data provided in Volume 1.3, Pages 126 and 127, the

b. Please explain the breadth of the specification This does not correlate with the specific gravity specifications

5. Regarding the packaging of the drug substance:

a. Please provide the actual name used in the 21 CFR 177.2600 citation which corresponds used for . No such listing can be found.

b. Please provide information

6. Regarding the stability information for the drug substance:

Please provide the data from the stability studies for the bulk drug substance carried out according to the revised protocols submitted in this amendment.

7. Regarding the manufacture of the drug product:

g. Please provide a revision in the Master Batch Record to include reference to the "Packaging and Labeling Instructions."

8. <u>Regarding the expiration date for the drug product</u>:

Please be advised that your request for an expiration date of 24 months is not acceptable. Since the drug product
the expiration date can only be extended for six months past the actual data provided, and an expiration date of 18 months is granted.

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ 3/16/98 /S/ 3/16/98

Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-772
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Shaw
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: mm/March 10, 1998/c:\wpfiles\cso\n\20772803.ir
Initialed by: EDuffy 3/12/98
LTalarico 3/13/98
final: March 16, 1998

INFORMATION REQUEST (IR)

MEMORANDUM OF TELECON

DATE: March 11, 1998

APPLICATION NUMBER: NDA 20-772; Sucraid (sacrosidase) Oral Solution

BETWEEN:

Name: Dayton Reardan, Ph.D.
Phone: (612) 513-6969
Representing: Orphan Medical, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Post-Marketing Surveillance Proposal

BACKGROUND: NDA 20-772 was submitted May 6, 1997 by Orphan Medical, Inc. and provides for Sucraid Oral Solution in the treatment of the genetically determined sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID). The application was Approvable (AE) November 6, 1997 pending the resolution of chemistry, manufacturing, and controls and microbiology deficiencies, along with final printed labeling (FPL).

The firm responded to the AE letter in a December 12, 1997 submission. At a January 7, 1998 team meeting Dr. Talarico requested that the firm be asked to provide follow up information on the first 50-100 patients to receive Sucraid post approval, due to the compound's potential to cause an allergic hypersensitivity reaction. On February 17, 1998 the firm submitted their proposal for a post-approval surveillance program (see attachment A). This proposal was consulted to Dr. Diane Wysowski, Epidemiologist (see Epidemiology review of sponsor's proposal, dated March 3, 1998; attachment B).

TODAY'S PHONE CALL: At Dr. Talarico's request, I called the sponsor and informed them that their post-approval surveillance proposal was acceptable as submitted. However, I conveyed the Agency's concern, as expressed in the March 3, 1998 epidemiology review, that although the firm's proposal includes a registry of all patients who will be administered Sucraid, it lacks <u>active</u> follow-up of these patients. At Dr. Talarico's suggestion, I asked the firm to consider the addition of an active follow-up component to their proposal, such as including a postcard with a standard questionnaire to evaluate patient tolerability in each package of the drug product. In response, Dr. Reardan agreed to consider this request, as well as other measures which would ensure active follow-up of all Sucraid patients, and the call was concluded.

/S/ 3/26/98

Melodi McNeil
Regulatory Health Project Manager

Attachments:

A. Firm's proposal
B. March 3, 1998 Epidemiology review

cc: Original NDA 20-772
HFD-180/Div. File
HFD-180/McNeil
HFD-180/Talarico
HFD-180/Gallo-Torres
HFD-733/Wysowski
RD Init: KJohnson 3/25/98
Final: March 26, 1998
TELECON

Attachment A
Firm's Proposal

COPY

DUPLICATE

ORPHAN MEDICAL

February 17, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 19 1998
HFD-180

Lilia Talarico, M.D.
Division of Gastrointestinal & Coagulation Drug Products
Center for Drug Evaluation and Research [HFD-180]
Food and Drug Administration
Division Document Room 6B24
5600 Fishers Lane
Rockville, MD 20857

APPEARS THIS WAY ON ORIGINAL

SUBJECT: **NDA 20-772, Sucraid™ (sacrosidase) Oral Solution, Orphan Drug Designation 93-786, Proposed Post-approval surveillance**

APPEARS THIS WAY ON ORIGINAL

Dear Dr. Talarico:

This letter is in response to a request from Melodi McNeil of your division for Orphan Medical to explain our planned post approval surveillance system to ensure that any adverse experiences are appropriately reported to FDA.

Congenital Sucrase-Isomaltase Deficiency (CSID) is a rare disease in the United States. Our market projections currently estimate on the order of 100 to possibly as high as five hundred patients with CSID of severe enough etiology to require replacement enzyme therapy. Dr. William Treem, of whom every physician with one of these patients appears to be aware, has been approached for less than 100 referrals over the last many years. He is currently aware of about 50-60 patients who would immediately make use of Sucraid once it becomes available on the market. Given the nature of CSID, Orphan Medical plans to distribute Sucraid only through a central pharmacy. This means that Sucraid will only be available from

Orphan Medical will be very interested in finding as many patients as possible to keep the costs of this product reasonable for the health care system in the United States.

Each patient is so captured in a patient registry at . If a patient in this system stops ordering Sucraid, or orders less frequently than their dosing regimen dictates, a contact would be made by

Inc. to determine the reason the patient is not compliant. Orphan Medical would therefore be building a database. If a patient is precluded from treatment due to a hypersensitivity reaction, such information would be captured and reported to Orphan Medical.

In addition to the specific program outlined above, Orphan Medical has a professional services group staffed by pharmacists (Pharm.D.). Anyone can call our toll free number to report adverse events, complaints, problems, or ask for advice and assistance. This phone number is staffed 24 hours a day, seven days a week and is a key component of our post marketing surveillance for all of our products which have been approved for marketing in the United States by the Food and Drug Administration.

In summary, Orphan Medical believes that given the very small patient population, distribution through a central pharmacy, development of a patient registry, institution of a patient compliance program as well as our contacts with Dr. Treem, other metabolic physician specialists along with our existing post-approval toll free professional services function that we will capture any issues, problems or benefits for patients using Sucraid.

Please feel free to call me should this letter not provide sufficient assurance that Orphan Medical will be actively monitoring the patients who will be benefiting from the commercial availability of Sucraid.

Sincerely yours,

Dayton Reardan

Dayton Reardan, PhD, RAC
Vice President of Regulatory Affairs
Direct phone (612) 513-6969

cc: Melodi McNeil, [HFD-180] by FAX (301) 443-9285

r:\sucrase\postnda\fda28.doc

Attachment B

March 3, 1998 Epidemiology Review

MEMORANDUM

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

DATE: March 3, 1998

FROM: Diane K. Wysowski, Ph.D., Epidemiologist, Division of Pharmacovigilance and Epidemiology, HFD-733

THROUGH: Ralph Lillie, R.Ph., M.P.H., Acting Director, Division of Pharmacovigilance and Epidemiology, HFD-730 DGraham for RLillie 3/3/98

TO: Lilia Talarico, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Phase 4 postmarketing study of patients exposed to Sucraid

On February 27, 1998, I received a request for consultation from Melodi McNeil, Project Manager, HFD-180, asking that I review a postmarketing surveillance proposal for Sucraid. This proposal was submitted by Orphan Medical, Inc., the sponsor of Sucraid, in response to a request by Melodi McNeil for a protocol for a phase 4 postmarketing study of hypersensitivity reactions in patients exposed to Sucraid. In a meeting on February 12, 1998, Drs. Lilia Talarico and Hugo Gallo-Torres, Ms. McNeil, and myself discussed the need for, and possible design of, a Phase 4 postmarketing study. We concluded that such a study was probably justified unless the sponsor could provide additional information concerning the asthmatic child who developed severe wheezing after having received Sucraid in a clinical trial that would reassure us that the drug was unlikely to be associated with the reaction. We decided that, since the number of patients with congenital sucrase-isomaltase deficiency for which the drug is indicated is likely to be small, a registry with active follow-up of cases would be a possible mechanism to study the incidence of hypersensitivity reactions in patients administered Sucraid. We acknowledged that a registry with active followup of patients suffered from the lack of a placebo control group so that neither we nor the sponsor would be able to compare the incidence of hypersensitivity reactions in patients with congenital sucrase-isomaltase deficiency in individuals exposed and not exposed to the drug. However, Drs. Talarico and Gallo-Torres did not believe a clinical trial or extension of the clinical trial was indicated at this time. We also discussed the possibility of screening patients for reaction to injection of yeast prior to administration of Sucraid, but Dr. Talarico pointed out that there might be a high rate of false positives.

The postmarketing surveillance proposal submitted indicates that Sucraid will only be available from which will process prescriptions (apparently submitted by physicians) and ship Sucraid by air mail directly to the patient or the patient's parents. Each patient would then be captured in a patient registry at If a patient stops ordering Sucraid or orders less that his/her prescribed dosing regimen, the patient would be contacted to determine the reason for drug discontinuation or non-compliance. If a patient stops taking the medication due to a hypersensitivity reaction, the information would be reported to Orphan Medical. Also, Orphan Medical has a toll-free telephone number so that adverse events can be phoned in 24 hours per day, seven days per week.

While this proposal includes a registry of patients, no ACTIVE followup of patients would be performed by the company. There are several problems associated with the passive surveillance the sponsor proposes:
1)Although the company will be relying on notification of discontinuation of Sucraid for notification of death or other serious reaction, the report may not be timely, especially when large supplies of drug are leftover. For hypersensitivity reactions that occur shortly after drug administration, knowledge of the reaction as soon as possible after the reaction occurs could conceivably result in regulatory action or identification of risk factors (e.g., asthma or allergy to specific allergens) which could prevent others from receiving the drug and developing the reaction.
2)If the patient is first administered Sucraid in the doctor's office and experiences a reaction there, the patient would not become part of the registry of patients prescribed the drug unless the doctor reports the administration of the medication and the reaction.
3)If the reaction is not serious enough for the patient to seek medical attention (as with the development of a rash) or is believed to be part of an underlying disease (such as wheezing in an asthmatic patient), the patient may not associate the event with the drug and would not report it to the prescribing physician or reporting system.
4)With passive reporting systems, information about the patient and the clinical circumstances of the adverse event necessary for an assessment of causality are frequently omitted or not reported in a standardized fashion.

For these reasons, I would recommend that the sponsor set up ACTIVE surveillance of the first 100 persons (at a minimum) prescribed Sucraid. A sample size of 100 would be required to detect an adverse event occurring in >3% of subjects while a study size of 300 would be required to detect an adverse event occurring in >1% of subjects. Active surveillance could be performed by interviewing the parent (preferably the mother) of the patient prescribed the drug by telephone with a standardized questionnaire after some specified duration of treatment (for timeliness, I would recommend no later than one week) following receipt of the medication. For this, the company would need to notify the family at the time of Sucraid prescription that a representative of the company will be calling to obtain information about how the medication "agrees" with the patient. The company would need to have submitted to them at the time of prescription the name of the parent and phone number(s) at which she/he could be reached.

Alternatively, each prescribing physician could be contacted about each patient, but this would place an undue burden on a few physicians since the drug is not widely prescribed. Also, with this method of followup through physicians, as stated previously, the sponsor would not ascertain events/reactions (such as a rash) which were not brought to the prescribing physician's attention. The sponsor might be able to propose some other acceptable method of active followup of each patient; I would be glad to discuss approaches with them before they resubmit a revised plan.

/S/

Diane K. Wysowski, Ph.D.

cc:Gallo-Torres/McNeil/HFD-180
Lillie/HFD-730 /S/ 3/4/98
Wysowski/Graham/Chron/Sucraid file/HFD-733
Pamer/Piazza-Hepp/Barash/HFD-735

/S/ 3/3/98

NDA 20-772

Orphan Medical, Inc.
Attention: Dayton Reardan, Ph.D.
13911 Ridgedale Drive
Minnetonka, MN 55305

SEP 22 1997

Dear Dr. Reardan:

Please refer to your pending May 6, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sucraid™ (sacrosidase) Oral Solution.

We also refer to your amendments dated June 16, July 1, July 18, August 20, and September 11 1997.

To complete our review of the chemistry, manufacturing and controls section of your submission, we request the following information:

I. Regarding Drug Substance:

A. <u>Description and Characterization:</u>

Redacted 13

pages of trade

secret and/or

confidential

commercial

information

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours,

/S/ 9/18/97

/S/ 9/18/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-772
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Shaw
HFD-160/Hughes
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: mm/September 10, 1997/c:\wpfiles\cso\n\20772709.ir
Initialed by: AShaw 9/10/97, 9/12/97, 9/18/97
EDuffy 9/17/97, 9/18/97
final: September 18, 1997

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

NDA 20-772

Orphan Medical, Inc.
Attention: Dayton Reardan, Ph.D.
13911 Ridgedale Drive
Minnetonka, MN 55305

JUL 31 1997

Dear Dr. Reardan:

Please refer to your pending May 6, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sucraid (sacrosidase) Oral Solution.

To continue our review of the microbiology section of your submission, we request that you

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/

/S/ 7/30/97
7/31/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
- Original NDA 20-772
- HFD-180/Div. Files
- HFD-180/CSO/M.McNeil
- HFD-180/Talarico
- HFD-180/Shaw
- HFD-160/Hughes
- HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: mm/July 30, 1997/c:\wpfiles\cso\n\20772707.ir
final: July 30, 1997

INFORMATION REQUEST (IR)

NDA 20-772

Orphan Medical, Inc.
Attention: Dayton T. Reardan, Ph.D.
13911 Ridgedale Drive, Suite 475
Minnetonka, MN 55305

JUL - 7 1997

Dear Dr. Reardan:

Please refer to your pending May 6, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sucraid (sacrosidase) Oral Solution.

We also refer to your amendment dated June 16, 1997.

To continue our review of the chemistry, manufacturing, and controls section of your submission, we have the following requests:

APPEARS THIS WAY ON ORIGINAL

1. Please submit an executed batch record.

2. Completely describe and provide the validation report for the

3. Please explain the operation Your explanation should include a description of the flow of all materials and indicate which are involved in the

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

APPEARS THIS WAY ON ORIGINAL

/S/ 7-7-97 /S/ 7/7/97

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

cc:
Original NDA 20-772
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Shaw
HFD-820/ONDC Division Director (only for CMC related issues)
Drafted by: mm/June 30, 1997/c:\wpfiles\cso\n20772706.ir
Initialed by: EDuffy 7/1/97
final: July 7, 1997

INFORMATION REQUEST (IR)

McNeil

NDA 20-772

JUN - 4 1997

Orphan Medical, Inc.
Attention: Dayton T. Reardan, Ph.D.
13911 Ridgedale Drive, Suite 475
Minnetonka, MN 55305

Dear Dr. Reardan:

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: Sucraid (sacrosidase) Oral Solution

Therapeutic Classification: Priority

Date of Application: May 6, 1997

Date of Receipt: May 7, 1997

APPEARS THIS WAY ON ORIGINAL

Our Reference Number: 20-772

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 July 6, 1997 in accordance with 21 CFR 314.101(a).

If you have any questions concerning this NDA, please contact me at (301) 443-0483.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

/S/ 6/3/97

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

cc:
Original NDA 20-772
HFD-180/Div. Files
HFD-180/CSO/M.McNeil

DISTRICT OFFICE

Drafted by: mm/June 3, 1997/c:\wpfiles\cso\n\20772706.ack
Final: June 3, 1997

ACKNOWLEDGEMENT (AC)

MEMORANDUM OF TELECON

DATE: June 27, 1997

APPLICATION NUMBER: NDA 20-772; Sucraid (sacrosidase) Oral Solution

BETWEEN:

Name: Dayton Reardan, Ph.D., Regulatory Affairs
Phone: (612) 513-6969
Representing: Orphan Medical, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Facilities Ready for Inspection

APPEARS THIS WAY ON ORIGINAL

BACKGROUND: NDA 20-772 was submitted May 6, 1997 and provides for Sucraid Oral Solution in the treatment of confirmed or suspected congenital sucrase-isomaltase deficiency (CSID).

TODAY'S PHONE CALL: In response to my question, Dr. Reardan confirmed that each manufacturing facility cited in the NDA

The call was concluded.

/S/ 7/15/97

Melodi McNeil, Project Manager
Regulatory Health Project Manager

APPEARS THIS WAY ON ORIGINAL

cc: Original NDA 20-772
HFD-180/Div. File
HFD-180/Melodi McNeil, Project Manager
HFD-180/AShaw
HFD-180/EDuffy

APPEARS THIS WAY ON ORIGINAL

TELECON

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

DA/PLA/PMA # 20-772 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Sucraid (sacrosidase) Oral Solution Action: AP AE NA

Applicant Orphan Medical, Inc. Therapeutic Class enzyme replacement

Indication(s) previously approved none

Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Proposed indication in this application genetic sucrase deficiency which is part of CSID (congenital sucrase-isomaltase deficiency)

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X Yes (Continue with questions) __ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

X Neonates (Birth-1month) X Infants (1month-2yrs) X Children (2-12yrs) X Adolecents(12-16yrs)

X 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __ c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**

- __ a. Pediatric studies are needed.
- __ b. Pediatric studies may not be needed but a pediatric supplement is needed.

APPEARS THIS WAY ON ORIGINAL

__ 6. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ , Project Manager 2/10/98

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-772
HFD-180 /Div File
NDA/PLA Action Package
HFD-006/ KRoberts
HFD-180/ McNeil

APPEARS THIS WAY ON ORIGINAL

(revised 9/15/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-772 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 180 Trade and generic names/dosage form: Sucraid (sacrosidase) Oral Solution Action: AP AE NA

Applicant Orphan Medical, Inc. Therapeutic Class enzyme replacement

Indication(s) previously approved none

Pediatric information in labeling of approved indication(s) is adequate X inadequate ___

Indication in this application genetic sucrase deficiency which is part of CSID (For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

APPEARS THIS WAY ON ORIGINAL

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Project Manager
Signature of Preparer and Title

10/2/97
Date

APPEARS THIS WAY ON ORIGINAL

cc: Orig NDA/PLA/PMA # 20-772
HFD-180 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ORPHAN MEDICAL

September 11, 1997

Lilia Talarico, M.D.
Division of Gastrointestinal & Coagulation Drug Products
Center for Drug Evaluation and Research [HFD-180]
Food and Drug Administration
Division Document Room 6B24
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: **NDA 20-772, SUCRAID™ (sacrosidase) ORAL SOLUTION, Environmental Assessment Claim for Categorical Exclusion**

Dear Dr. Talarico:

In light of the new regulations published in the July 29, 1997 Federal Register and promulgated under the National Environmental Policy Act, we respectfully request withdrawal of the Environmental Assessment submitted in the May 6, 1997 original submission of the above referenced New Drug Application.

The requested action, approval of NDA 20-772, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(b). To Orphan Medical's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

Please contact me at (612)513-6969 if any further information is required.

Sincerely yours,

Dayton Reardan

Dayton Reardan, PhD, RAC
Vice President of Regulatory Affairs

cc: Melodi McNeil (letter only), [HFD-180] by FAX (301) 443-9285

BEST POSSIBLE COPY