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Briefing Package

Petition (PP 97-1) to Exempt Sucraid™ from the Special
Packaging Requirements for Oral Prescription Drugs

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Products Identified
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Firms Notified.

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Executive Summary

On July 10, 1997, Orphan Medical petitioned the Commission to exempt Sucraid™, an oral prescription drug, from special packaging requirements. Sucraid™ is a new liquid formulation of sacrosidase, a yeast derived form of the sucrase enzyme, used for the treatment of congenital sucrase-isomaltase deficiency (CSID). The FDA approved a New Drug Application for Sucraid™ on April 10, 1998.

As an oral prescription drug, Sucraid™ requires special or child-resistant packaging under 16 CFR 1700.14 (10) of the Poison Prevention Packaging Act (PPPA). However, the PPPA provides procedures for seeking an exemption from special packaging requirements. The petitioner must justify the exemption based on the following grounds: 1) the lack of toxicity and lack of adverse human experience; 2) special packaging is not technically feasible, practicable, and appropriate; or 3) special packaging is incompatible with the particular substance.

The petitioner stated that the justification for the exemption is based on: 1) the lack of toxicity and adverse human experience associated with Sucraid™; and 2) their argument that special packaging is not technically feasible, practicable, or appropriate. The enzyme in Sucraid™ is not expected to be inherently toxic because it is a glycoprotein that will be digested to amino acids like other dietary proteins. The only available toxicity information derives from studies performed by the petitioner who argues that clinical experience with Sucraid™ in patients five months old and greater has not shown evidence of significant toxicity or intolerance. Of 52 patients, only one withdrew from the studies because of an adverse event. A child experienced an acute hypersensitivity reaction to Sucraid™ which resolved without sequelae. The petitioner asserts that other reported adverse events considered by the investigator to be possibly related to Sucraid™ (e.g. diarrhea, abdominal pain, etc.) were generally minor and are frequently associated with CSID, the disease this drug is used to treat. Additionally, no cases of intentional or accidental overdose of Sucraid™ have been reported.

Although the petitioner states that special packaging is not technically feasible, practicable, or appropriate for Sucraid™, the staff did not consider this argument in making its recommendation because the lack of significant toxicity associated with Sucraid™ was sufficient grounds. Based on available information, the staff recommends that the Commission grant the petition and propose a rule to exempt Sucraid™ and similar products, that contain the enzyme sacrosidase (sucrase) in a solution of glycerol and water, from the special packaging requirements of the PPPA.



United States
CONSUMER PRODUCT SAFETY COMMISSION
Washington, D.C. 20207

MAY 20 1998

To: The Commission
Sadye E. Dunn, Secretary

Through: Jeffrey S. Bromme, General Counsel *JS*
Through: Pamela Gilbert, Executive Director *PG*

From: Ronald L. Medford, Assistant Executive Director for Hazard Identification *RLM*
and Reduction
Jacqueline N. Ferrante, Ph.D., Pharmacologist, Directorate for Epidemiology *JF*
and Health Sciences, Division of Health Sciences

Subject: Petition (PP 97-1) to exempt Sucraid™ from the special packaging requirements for oral prescription drugs

I. Introduction

Oral prescription drugs require special or child-resistant packaging under 16 CFR 1700.14 (10) of the Poison Prevention Packaging Act (PPPA). However, the PPPA provides procedures for seeking an exemption from special packaging requirements. The petitioner must justify the exemption based on the following grounds: 1) the lack of toxicity and lack of adverse human experience; 2) special packaging is not technically feasible, practicable, and appropriate; or 3) special packaging is incompatible with the particular substance. In the past, the Commission granted exemptions to oral prescription drugs such as prednisone, erythromycin, and conjugated estrogen tablets that met one or more of these criteria.

II. Petition

In a letter dated July 10, 1997, Orphan Medical petitioned the Commission to exempt Sucraid™ from the special packaging requirements for oral prescription drugs under the PPPA (Tab A). As an oral prescription drug, Sucraid™ is required to be in child-resistant packaging (CRP). The petitioner states that its exemption request is based on the lack of toxicity and adverse human experience associated with Sucraid™ and states that "special packaging is not technically feasible, practicable, or appropriate for the substance." Sucraid™ is a liquid formulation of sacrosidase, a yeast derived form of the sucrase enzyme. This enzyme has been used extensively in the confectionery and baking industry as a flavoring agent and adjuvant at a level not to exceed five percent in food. Under 21 CFR 170.30 it is a "Generally Recognized as

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Initial *rh* Date *5/20/98*

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Products Identified
Excepted

Safe"(GRAS) food material because of "its long history of safe use in human food." According to the petitioner, there is no reported toxicity associated with the use of the enzyme in food products.

The Food and Drug Administration (FDA) designated Sucraid™ an Orphan Drug on December 10, 1993 under section 316.20 of the Food, Drug, and Cosmetic Act. Orphan drugs are intended to be used for rare diseases or conditions which either 1) affect fewer than 200,000 people in the U.S. or 2) affect more than 200,000 in the U.S. but there is no reasonable expectation that the cost of developing and making the drug will be recovered from sales in the U.S. Sucraid™ is intended for patients with congenital sucrase-isomaltase deficiency (CSID). It is an enzyme replacement therapy for sucrase, not isomaltase. Orphan Medical submitted a New Drug Application (NDA) for Sucraid™ to the FDA on May 6, 1997. Sucraid™ was approved on April 10, 1998. Approval will not be given to another sponsor of the same drug for the same indication for seven years except as provided by law. Sucraid™ has not been marketed outside the U.S.

A. Congenital Sucrase-Isomaltase Deficiency (CSID)

CSID is an inherited disease characterized by reduced or absent levels of sucrase and isomaltase, two enzymes normally produced in the small intestine. CSID is rare in most populations, but the prevalence may be underestimated because some patients are undiagnosed. The prevalence of CSID is 0.2% in North Americans and higher in Eskimos. The petitioner estimates that there are approximately 3,000 to 10,000 cases in the U.S.

Normally, sucrase breaks sucrose (table sugar) down into glucose and fructose. Patients with CSID are unable to digest and absorb sucrose resulting in symptoms including diarrhea, gas, bloating, and abdominal pain. CSID has been diagnosed in both infants and adults. Undiagnosed infants with CSID may have severe, protracted diarrhea associated with failure to thrive. A small number of patients with severe cases of CSID require hospitalization for diarrhea and dehydration, malnutrition, weakness, and muscle wasting.

The current treatment of CSID involves elimination of sucrose from the diet, but this may be difficult for most patients to maintain. Enzyme replacement therapy is another alternative and was initially tried with fresh or lyophilized baker's yeast which naturally contains sucrase. The baker's yeast successfully reduced or eliminated symptoms associated with CSID without any reported adverse effects. Sucraid™ is another option for patients with CSID who want to consume sucrose.

B. Product Description

Sucraid™ is a palatable liquid formulation of sucrase that is derived from baker's yeast. It contains 8,500 International Units (~ 1.5 milligrams of protein) per milliliter (ml) of the enzyme in a 50:50 solution of glycerol and water. Sucraid™ is contraindicated in patients known to be hypersensitive to yeast, yeast products, and glycerol. The recommended dose of Sucraid™ is one

ml per meal or snack for patients weighing up to 15 kilograms (kg) (33 pounds) and 2 ml for patients over 15 kg. The dose should be diluted in 2 to 4 ounces of water, milk, or infant formula.

Sucraid™ is packaged in a hermetically sealed plastic 118 ml bottle with a threaded top and a dropper tip that are compatible with the cap. The cap has a small spike on the inside which is used to pierce the sealed tip when the product is first used. The product is sold in a paperboard carton that contains two bottles of liquid with a measuring scoop. The manufacturer recommends refrigeration of Sucraid™ and that unused portions be discarded four weeks after opening because of the potential for bacterial growth.

C. Animal Data

Animal testing was not required to assess the toxicity of Sucraid™ because of the availability of the yeast-derived enzyme as a food grade product. Orphan Medical requested a waiver of nonclinical pharmacology tests from the FDA based on: 1) the nature of the enzyme as a replacement for a missing endogenous one; 2) a clear demonstration of the efficacy of the enzyme in humans; and 3) the unavailability of appropriate animal models for CSID. According to the petitioner, pharmacokinetic¹ and LD50² studies of Sucraid™ were not performed based on its lack of toxicity, the extensive database of use in humans, and its long-term use in the baking and confectionery industry.

D. Human Experience Data

There have been three human clinical trials of Sucraid™. Two are complete and one of these has been published in the medical literature. Clinical investigators conducting these trials determined that none of the reported adverse effects were probably or definitely related to Sucraid™. The majority of adverse events were described as either symptoms of a concurrent illness common in children (e.g., flu, upper respiratory infection, or otitis media) or GI symptoms routinely associated with CSID (e.g., diarrhea, nausea, vomiting, or abdominal pain).

The first trial (S-1) was published in the medical literature. The aim of this study was to determine the effect of Sucraid™. The study demonstrated the efficacy of Sucraid™. Most patients ingesting 1 ml of the most concentrated dose (1:100 dilution) of the enzyme with each meal experienced minimal symptoms, whereas symptoms of diarrhea, abdominal pain, and excessive gas were more prevalent with increasing dilution of the enzyme, indicating that the symptoms were CSID-related, not Sucraid™-related. Eight of 14 patients had at least one adverse event including fever, flu, headache, vomiting, congestion, side pain, runny stools, rectal bleeding, and ear problems. A total of 17 adverse events were reported, eight were considered by the investigator to be related to a concurrent illness and nine were rated as unknown or unrelated

¹ The absorption, distribution, metabolism, and excretion of a substance.

² Median lethal dose.

to the drug. No adverse events were rated as possibly or probably drug-related. There were no serious adverse events or withdrawals due to adverse events during the trial. Four patients withdrew from trial S-1 after treatment. These patients were lost to follow-up.

The second trial (S-2) examined Sucraid™'s ability to prevent or reduce breath hydrogen excretion in CSID patients after a large dose of sucrose and to prevent GI symptoms associated with a normal sucrose-containing diet. Twenty-six of 34 patients experienced at least one adverse event in this trial. Most of the adverse events (52%) were attributed to concurrent illnesses and the investigator considered these to be unrelated to the enzyme. Included were 12 patients who experienced symptoms including fever, cough, sore throat, runny nose, diarrhea, cramping, and abdominal pain. These symptoms were due to illnesses common in children including viral infection/flu, ear infection, and strep throat.

Eleven of the 26 patients who experienced adverse events in trial S-2 had one or more adverse events that the investigator considered possibly related to Sucraid™. Symptoms included abdominal pain, diarrhea, nausea, vomiting, constipation, dehydration, cramps, headache, insomnia, nervousness, and wheezing. The petitioner noted that many of these symptoms (e.g., abdominal pain, diarrhea, nausea, and vomiting) are typical of CSID. The expression of symptoms in CSID patients may vary depending on a number of factors including residual endogenous enzyme activity, gastric emptying rate, and the metabolic activity of colonic bacteria. Therefore, a particular dose of Sucraid™ may not have been sufficient to relieve all of the symptoms. Most of the patients tolerated the enzyme well enough to complete both phases of the trial.

There were no deaths in trial S-2. Of six patients who withdrew from trial S-2, only one withdrew because of an adverse event. This patient, a 48-month-old male, started wheezing 90 minutes after receiving a dose (2 ml) of the full strength enzyme. He was taken to the emergency room, admitted to the intensive care unit, and was discharged the following day. The child's history of asthma and steroid treatment were not reported to the clinical investigator or trial coordinator prior to the trial. The child was rechallenged with Sucraid™ and the skin test was positive.

There were three other patients who experienced adverse events defined as serious in trial S-2. A serious adverse event was defined as "any event that was fatal or life-threatening, was permanently disabling, required inpatient hospitalization (or an emergency room visit without hospitalization), or was a congenital anomaly, cancer, or overdose." In one case a 6-month-old female patient had elective surgery for closure of a colostomy. This event had no relationship to Sucraid™. In a second case an 8-month-old female was treated for otitis media with an antibiotic 13 days after starting Sucraid™ treatment. The child vomited immediately following a dose of antibiotic after dinner. Two days later she was admitted to an emergency room with symptoms of projectile vomiting, gray skin, and white lips which the investigator considered to

be possibly related to Sucraid™. Nevertheless, the patient completed the trial and continued on open-label³ Sucraid™ with meals and snacks.

Finally, a 47-month-old male became dehydrated after Sucraid™ treatment and was admitted to the hospital for rehydration. The investigator considered that this event was possibly related to Sucraid™. Subsequently, this child completed the trial and continued taking Sucraid™ with meals and snacks. Therefore, in only two of these three cases were there events that were possibly related to Sucraid™. In both cases the patient completed the trial and continued to use the product as needed.

E. Toxicity

The enzyme in Sucraid™ is a glycoprotein with a known amino acid sequence. One bottle of sucraid (118 ml) contains the equivalent of 150 mg or 0.15 g of protein. This is a small fraction of total dietary protein in humans which is usually about 125 g/day. The petitioner reasoned that no direct systemic toxicity from the enzyme in Sucraid™ is possible because it would not be absorbed intact due to its large molecular size. As with other proteins ingested in the diet, it will be digested in the GI tract to polypeptides and subsequently to its constituent amino acids. These amino acids would not be expected to cause toxicity because they are used to synthesize new protein or are burned for energy.

The enzyme in Sucraid™ is dissolved in a 50:50 solution of glycerol (or glycerin) and water. Glycerol is a sweet syrupy liquid valued for its solvent, preservative, and moisturizing properties. It is "Generally Recognized as Safe" by the FDA as a food for human consumption (21 CFR 182.1320). Pharmacologically, glycerol is classified as an osmotic diuretic which is used to reduce intraocular and intracranial pressure. The usual dose of glycerol for reducing intraocular pressure is 1 to 2 g/kg given as a 50% or 75% solution. Additional doses of 0.5 g/kg may be given if required. Glycerol is also classified as a hyperosmotic laxative and may be given rectally as a suppository or solution in single doses.

The petitioner identifies glycerol as the most toxic component of the product. Human toxic or lethal doses of glycerol have not been defined. Adverse effects associated with glycerol include nausea, vomiting, headache, and dehydration. Less frequently reported effects include diarrhea, thirst, dizziness, and mental confusion. Hemolysis⁴, hemoglobinuria⁵, and renal damage have been documented with intravenous (IV) administration of glycerol at doses of 0.5 to 2 g/kg. Additionally, high risk patients, (e.g. those with cardiac failure, renal or hepatic disease, dehydration, diabetes, and hypervolemia) may be sensitive to the effects of glycerol. In these

³Open label means that patients are given Sucraid who need it. It is not part of the clinical trial.

⁴The destruction of red blood cells.

⁵The presence of hemoglobin in the urine.

subjects, glycerol may cause circulatory overload, pulmonary edema, congestive heart failure, hyperglycemia, and hyperosmolar nonketotic coma.

The petitioner calculated that a four ounce bottle of Sucraid™ contains about 71 grams of glycerol, which is equivalent to a dose of 7.1 g/kg in a 10 kg child. Although more serious effects have been described following IV glycerol treatment or in high risk patients, the Hazardous Chemicals Desk Reference⁶ indicates that glycerol is mildly toxic by ingestion. The petitioner also cited a prescription drug product, Osmoglyn, which is a pre-surgical 50% solution of glycerol used to reduce intraocular pressure. The toxicologic management for Osmoglyn in the Poisindex®⁷ categorizes it as a non-toxic ingestion. According to the Poisindex®, "materials referenced to this management have been considered very unlikely to produce any toxicity except in enormous doses."

Additionally, the Handbook of Common Poisonings in Children⁸ categorizes glycerol as a laxative and states that "acute exposure to most laxatives produces nausea, vomiting, and diarrhea, which are usually mild and self-limiting." Typically, the only treatment required after a single severe exposure to laxatives is observation and fluid replacement, if needed. The staff identified three ingestion cases in children under five years old in the National Electronic Injury Surveillance System (NEISS) database that involved products that contain glycerol. The products ingested were a glycerol suppository, a baby enema preparation, and an ear solution. In all three cases the disposition was defined as treated and released, or examined and released without treatment.

Based on available information, there is no evidence that Sucraid™ causes significant toxicity. No adverse reaction reports were filed under 21 CFR 314.80 at the time the petition was submitted and there have been no reports of intentional or accidental overdose of Sucraid™.

F. Packaging

While the petitioner stated that special packaging is not technically feasible, practicable, or appropriate, the staff did not rely on or evaluate this information. The apparent lack of serious toxicity associated with Sucraid™ was sufficient grounds for recommending an exemption.

G. Economic Information

The market for Sucraid™ is expected to be small given the estimated 3,000 to 10,000 patients with CSID in the U.S. Commercial sales figures are not available because of the recent approval of the product. Orphan Medical is a small manufacturer based on employment and

⁶Lewis, R.J. Sr., Hazardous Chemicals Desk Reference, Third Edition (Van Nostrand Reinhold, N.Y.), 1993.

⁷Poisindex® System. Rumack, B.H., Hess, A.J., & Gelman, C.R (Eds.). Micromedex, Inc., Englewood, Colorado, 1997.

⁸Handbook of Common Poisonings in Children, American Academy of Pediatrics, Third Edition, Rodgers, G.C. and Matyunas, N.J. (Eds.), 1994.

sales. The staff preliminarily concludes that an exemption for liquid sacrosidase (sucrase) products like Sucraid™ will not have a significant impact on the environment or on a substantial number of small businesses since Orphan Medical is the sole marketer of Sucraid™ and has marketing exclusivity for seven years.

H. Effective Date

When the Commission issues an exemption under the PPPA it typically becomes effective upon publication of the final rule in the Federal Register.

III. Options

- A. Grant the petition and propose a rule to exempt liquid sacrosidase (sucrase) products from special packaging requirements.

The Commission may grant the petition and propose rulemaking if it concludes that exempting these products will not present a risk of serious personal injury or illness to young children.

- B. Deny the petition.

The Commission may deny the petition if it concludes that there is insufficient evidence to show that these products would not be hazardous to young children if not packaged in special packaging.

- c. Defer the petition.

The Commission may defer the petition if it concludes that more information is needed to make a decision.

IV. Conclusion and Recommendation

There is no evidence that Sucraid™ would cause serious personal injury or illness to children who handle, use, or ingest it. No cases of intentional or accidental overdose of Sucraid™ have been reported. The only available toxicity information derives from studies conducted by the petitioner who argues that clinical experience with Sucraid™ in patients five months and greater has not shown evidence of significant toxicity or intolerance.

Fifty-two patients were treated with Sucraid™ in clinical studies up to a duration of 54 months. In only one case did a patient withdraw because of an adverse event. This involved an asthmatic patient who had an acute hypersensitivity reaction to Sucraid™ which resolved without sequelae. Adverse events that the clinical investigator determined to be possibly related to Sucraid™ and argued by the petitioner to be generally minor include abdominal pain, vomiting, nausea, diarrhea, constipation, insomnia, headache, nervousness, facial edema, and dehydration.

These effects are frequently associated with CSID, the disease Sucraid™ is used to treat. Notably, most of the patients tolerated the enzyme well enough to complete the studies.

Glycerol is another component of Sucraid™. Many of the known side effects of oral glycerol are minor and include headache, nausea, vomiting, and dizziness. The more serious adverse effects associated with glycerol are those observed in high risk patients or following IV administration. Moreover, the Poisindex® categorizes the management for a prescription product with the same percentage of glycerol as Sucraid™ as a non-toxic ingestion. Therefore, significant toxicity would not be expected from this ingredient.

Another consideration is that Sucraid™ will be used for a relatively small population (~ 3,000 to 10,000 patients) which limits the number of children exposed. Given all of the available information, the staff recommends that the Commission grant the petition and propose a rule to exempt products with the enzyme sacrosidase (sucrase) in a solution of glycerol and water. A draft FR notice is at Tab D.

TAB A

PP 97-1



Revised 1/30/97

CPSA & (b)(1) Cleared
No Mfrs/Prvblrs or
Products Identified
Excepted by 616 INDO
Firms Notified, EXCUSED
Comments Processed

July 10, 1997

Office of the Secretary
Consumer Product Safety Commission
Washington, DC 20207-0001

SUBJECT: Petition for Exemption from the Poison Prevention Packaging Act **Requirements** for the Prescription Drug **Sucraid™** (sacrosidase) oral **solution**

Dear Sir/Madam:

This petition for exemption from the Poison Prevention Packaging Act is being submitted under 16 CFR 1702. It requests exemption for the above referenced drug product from the special packaging requirements under 1700.14(a), specifically, 16 CFR 1700.14(a)(10). As requested by 16 CFR 1702.2, five (5) copies of this petition are enclosed herewith in addition to the original. Three (3) Sucraid investigational drug packages have been provided as requested.

A New Drug Application (NDA #20-772) for Sucraid (sacrosidase) oral solution was submitted under section 505(b) of the Food, Drug and Cosmetic Act (FD&C Act) on May 6, 1997. This medication has been designated an Orphan Drug under section 316.20 (number 93-786, designation date December 10, 1993). Sucraid is used for the treatment of congenital sucrase-isomaltase deficient patients (CSID) who are missing the endogenous digestive enzyme. The active moiety in Sucraid is sacrosidase, a yeast-derived form of the sucrase enzyme. Currently, there are no alternative drug treatments available for CSID patients numbering approximately 3,000 - 10,000 cases in the United States. Priority review status has been granted within the Food and Drug Administration. Priority review classification under the Prescription Drug User Fee Act of 1992 (PDUFA) determines the review time frame the application receives, which in this case is six months from the date of receipt (May 7, 1997). Based on priority review status, the lack of toxicity associated with sacrosidase oral solution, limited distribution of the product, and the medical necessity associated with the drug, Orphan Medical, Inc. has requested the Consumer Product Safety Commission to grant a stay of enforcement

for **Sucraid** until the process has been **completed** and this exemption from special packaging requirements can be reviewed and granted.

Under 16 CFR 1015.18, information that Orphan Medical, Inc. deems proprietary and trade secret is requested for exemption from disclosure under 5 USC 552(b) **(4)** is in bold print as follows:

The drug product is packaged in [REDACTED] plastic bottles which are blow-molded, **filled, and sealed.** Upon **sealing**, the bottle becomes a **self-contained** container/closure system. (A cap is included to assist in the opening of the bottle at the time of administration and for resealing the bottle for future use.)

The [REDACTED] cap is made of [REDACTED]. The cap is placed on the sealed bottle after filling. The cap has a small spike on the inside which can be used to pierce the sealed bottle tip at the time of first use. It cannot come in contact with the drug product until the bottle is opened. Labeling **requires** the product to be discarded four weeks after opening.

The scoop is made of white [REDACTED] which is composed of [REDACTED] resins. It is suitable for food contact use (21 CFR 177.1640). The scoop has no product contact except for measuring the dose. The scoop is placed between the two bottles in the carton.

We respectfully request the confidential information (highlighted in bold) not be maintained in the public file. Orphan Medical, Inc., however, intends in good **faith** to assist the Commission in the defense of any judicial proceeding that might thereafter be brought to compel the disclosure of information which the Commission has determined to be a trade secret or privileged or confidential commercial information.

JUSTIFICATION FOR THE EXEMPTION

The justification for the exemption,, required under 16 CFR 1702.3, is based on the following grounds:

- 1) the lack of need **for** special packaging to protect young children from serious injury or illness from the substance based on the lack of toxicity and lack of adverse human experience

and

- 2) special packaging is not technologically feasible, practicable, or appropriate for the substance.

1) JUSTIFICATION BASED UPON LACK OF NEED BASED ON LACK OF TOXICITY AND LACK OF ADVERSE HUMAN EXPERIENCE

Lack of Toxicity

Prior to the filing of NDA #20-772, Orphan Medical and FDA agreed that no nonclinical toxicity studies were required. This conclusion regarding sacrosidase's inherent lack of toxicity was based upon the following:

- (1) Yeast-derived sacrosidase has been widely utilized within the human food industry for decades in the confectionery and baking industry. It is a Generally Recognized as Safe (GRAS) food material under FDA provision 21 CFR § 170.30 due to its long history of safe use in human food. The sponsor is unaware of any reported toxicity associated with the use of sacrosidase as a food product.
- (2) Because sacrosidase is a large macromolecule, it will not be transported intact across the gastrointestinal mucosa and into the systemic circulation following oral ingestion. Thus, no systemic toxicity directly from the sacrosidase molecule is feasible.
- (3) Because sacrosidase is a naturally occurring enzyme with a glycoprotein structure, it will be digested to peptides and eventually amino acids within the small intestine. These metabolic products will be absorbed into the circulation and utilized as nutrients.
- (4) Several years of clinical experience with the yeast-derived oral sacrosidase solution in patients as young as 5 months of age have not revealed any evidence of significant toxicity or intolerance.

Orphan Medical has reviewed the scientific literature via computerized database searches and has determined that no studies have been published that examine the toxicity of the enzyme sucrase either endogenous human sucrase or exogenous yeast-derived sucrase.

Human Experience Data

In the development of most new drugs the new chemical entity is initially evaluated in biological screens (e.g. biochemistry, pharmacology, virology, microbiology) where an activity of interest is detected and measured. Over a period of time, and using several or many animal models, the scientists attempt to identify the specific compound with the greatest activity indicative of efficacy and the least toxicity. Usually a battery of in vitro and in vivo models are used in this endeavor and

thousands of compounds tested before a single compound is chosen for development. After a further one or more years of **preclinical** development the compound is eventually studied in humans.

Sucraid™ (sacrosidase) oral solution had a very different development path. Congenital sucrase-isomaltase deficiency **disease** (CSID) had been known for years before the logic of replacing the missing endogenous digestive enzyme **sucrase-isomaltase** was clinically attempted. The availability of the yeast-derived enzyme as a food grade product meant that animal testing was not required to assess its toxicity profile. Enzyme replacement in diseases such as **Gaucher's** Disease originally involved a difficult extraction of the enzyme from human tissue (placenta), but the enzyme sacrosidase was readily available from yeast manufacturers, and in fact is widely used by commercial bakeries, confection and candy makers.

The human evaluation of therapeutic efficacy was straightforward and the resulting efficacy data extremely clear cut and convincing. If an animal model of CSID existed, it would have been of interest to study Sucraid in this model, but no model does in fact exist.

Given the existence of substantial human data, there is no scientific need to retrospectively evaluate and measure the enzyme for its nonclinical efficacy. Other pharmacological tests were not deemed necessary because of safety data obtained in humans, the food status of the enzyme, and the large benefit to risk: ratio of the enzyme in patients with the rare disease congenital sucrase-isomaltase deficiency (**CSID**).

Sucraid consists of approximately 1.5 mg/mL of protein in an aqueous solution containing 50% glycerol and 50% water at an unbuffered slightly acidic **pH** of 4.6. This product is derived from baker's yeast (**saccharomyces cerevisiae**) and is the same formulation used extensively in the food and candy industry. The amounts utilized in such **products** as soft center chocolate coated cherries is a fraction (**<5%**) of the therapeutic amounts utilized to obtain the pharmacologic effect in patients with congenital sucrase-isomaltase deficiency. The protein contains a known amino acid sequence which is heavily glycosylated. The product contains no neurotropic or narcotic like compounds. It is metabolized to constituent amino acids and sugars in the digestive tract. There is no known or theoretical potential for abuse of this drug. The drug produces no **"high"** and while it **has** a mild sweet taste, it would certainly not be considered to produce a gastric high such as other sweet or chocolate based foods. Therefore, the likelihood of drug abuse is for all practical purposes is zero percent (0%).

Overdosage of the product has been considered by Orphan Medical. The most toxic component is the *glycerol* which makes up 50% of the product by weight and is an osmotic diuretic. The product provided in 4 ounce (118 mL) containers with a very small opening through which to obtain product. Should a child ingest the full contents of one bottle of Sucraid, they would receive the equivalent of 150 mg of protein, 59 mL of water, and 59 mL of glycerol. The 150 mg of protein and the 59 mL of water are negligible given even recommended daily requirements for infants. A full dose of 59 mL of glycerol into a two year old child weighing 10 kg would be the equivalent of $(59 \text{ mL}) \times (1.2 \text{ g/mL}) = 7.1 \text{ g/kg}$. The toxicity and safety of is deemed Generally Recognized as Safe (GRAS) by the Food and Drug Administration as a multiple purpose food substance in food for human consumption (21 CFR 182.1320). *Glycerol* is currently approved for use in multiple therapeutic products (Physicians Desk Reference 1996). The daily dose of the approved drug, OSMOGLYN, is 5 times that of the daily dose of Sucraid, per kg of body weight.

Therefore, if a child of 10 kg were to ingest the entire 4 oz. bottle of Sucraid, it is our assessment that there would be no significant toxic effect, particularly if the patient is kept hydrated. The proposed product labeling indicates the osmotic diuretic nature of the glycerol and the need for hydration should someone ingest an overdose of this product.

No cases of accidental or purposeful overdose have been reported but the protein chemical nature of the sacrosidase enzyme material and the fact that it is broken down in the intestinal tract following ingestion to nutrient peptides and amino acids supports the general principle that there is no significant toxicological effect.

Relevant Experimental Data

Three clinical trials have been conducted using Sucraid (sacrosidase) oral solution. None of the adverse events recorded at any time for patients during these three clinical trials were rated as probably or definitely drug-related by the clinical investigators. Although a number of adverse events were reported among these three trials, the vast majority fell into two categories: (1) they were symptoms of a concurrent illness common to the pediatric population such as flu, upper respiratory infections, or otitis media, or (2) they were GI symptoms commonplace to congenital sucrase-isomaltase deficiency (CSID) such as diarrhea, nausea, vomiting, or abdominal pain.

-4

Human Experimental Data Involving the Testing of *Human* Subjects

study S-1

The objective of this trial was to evaluate the effect of sacrosidase on breath hydrogen excretion and gastrointestinal symptoms following the ingestion of a large sucrose load, and to establish a dose range of sacrosidase which allows the consumption of a normal sucrose containing diet.

Patients were evaluated to confirm CSID diagnosis and trial eligibility prior to commencement of the breath hydrogen phase. During the breath hydrogen phase, patients were to undergo two **randomized** breath hydrogen tests, which entailed ingesting sucrose followed by placebo-or sacrosidase. During each test, and for a period of eight hours thereafter, gastrointestinal symptoms were to be recorded on a symptom diary. The breath hydrogen tests were to be separated by one week. During the dose-response phase, patients were instructed to maintain a normal sucrose diet while receiving each of four concentrations of sacrosidase (1:100 dilution, 1:1,000 dilution, 1:10,000 dilution, and 1:100,000 dilution) in random order, for a period of 14 days each. Stool frequency and consistency measures, as well as gastrointestinal symptoms, were to be recorded on a daily basis. Adverse events were collected throughout the trial.

Patients were dosed using a 14-day randomized crossover on each of 4 doses (dilutions) of liquid sacrosidase:

Treatment 1: 1:100 dilution
Treatment 2: 1:1,000 dilution
Treatment 3: 1:10,000 dilution
Treatment 4: 1:100,000 dilution

The dose used was 1 mL/meal or snack orally administered, added to 1 ounce of liquid (water, milk, juice, infant formula).

The breath hydrogen phase consisted of one week (two single doses given one week apart); the dose-response phase consisted of eight weeks (14 days on each of the four sacrosidase doses).

In the first trial (S-1) 8 of the 14 patients in the safety population experienced at least one adverse event. (See Table 8.8.4 below for details of adverse events). Symptoms associated with these events included fever, flu, headache, vomiting, congestion, side pain, runny stools, rectal bleeding, and ear problems. There were a total of 17 adverse events reported, eight of which were considered by the Clinical Investigator to be related to a concurrent illness while nine were rated as **unknown** or **were** not indicated to be drug related.

No adverse events were rated by the Clinical Investigator as possibly or probably drug related. There were no serious adverse events or withdrawals due to adverse events during this trial.

TABLE 8.8.4
 TRIAL S-1 (OMC-SUC-1): SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 1 of 2)

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
1/SW	Nausea/vomited	Nausea Vomit	BHT Placebo	NI	NI
	Lots of gagging	Vomit	BHT Enzyme	NI	NI
2/CB	Cold	Rhinitis	D/R 1:1,000	Cold medicine "Triaminic" given 1/2 tsp. x 3 days	NI
	Cranky, irritable	Nervousness	D/R 1:100	NI	NI
	Slight bleeding from rectum	Hem Pectal	D/R 1:100,000	NI	NI
4/BG	"caught viral and bad runny stools"	React Uneval Diarrhea	D/R 3:100	NI	Concurrent illness - not related'
8/DM	"achiness, sick, nausea"	Flu Synd	BHT Placebo	NI	NI
	Nausea	Nausea	BHT Enzyme	NI	NI
	"some bleeding from rectum with movement"	Hem Rectal	D/R 1:1000	"went away on its own"	NI

BHT = Breath Hydrogen Test Phase, D/R = Dose-Response Phase, NI = Not indicated

TABLE 8.8.4
 TRIAL S-f (OMC-SUC-1): SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 2 of 2)

Pt Number/ Initials	Adverse Event		Study Phase/ Tjc & Dose	Resolution of Adverse Event	Relationship to Study Drug
	(Original Term)	(COSTART term)			
8/DM	"side pain"	Pain Flank	D/R 1:10,000	"took muscle relaxants for cramps"	Concurrent illness - not related
9/CS	"fever, vomiting for a few days* "ear problems, congestion, left ear infection"	Fever Vomit Ear Die Rhinitis Infect	D/R 1:10,000 D/R 1:1,000	NI "gave her moxil"	Concurrent illness - not related Concurrent illness - not related
11/CK	Felt faint 2 hours after sucrose dose	Dizziness	BHT Placebo	NI	NI
13/JP	"had a stomach flu for a couple of days " "did not feel as well, ,did not eat as much, color and hair not as good as first bottle"	Flu Synd React Uneval Anorexia React Uneval	D/R 1:10,000 D/R 1:1,000	NI NI	Concurrent illness - not related NI
15/BE	Mild headache "flu Wed-Fri (Day 1,2,3), too much Halloween candy "	Headache Flu Synd , React Uneval	BHT Placebo D/R 1:100,000	NI NI	NI Concurrent illness - not related

BHT = Breath Hydrogen Test Phase, D/R = Dose-Response Phase, NI = Not indicated

Trial S-2

The objective of this trial was to test the efficacy of yeast-derived **liquid sacrosidase** in treating patients of all ages with congenital **sucrase-isomaltase deficiency (CSID)**. The specific hypotheses to be tested were: 1) sacrosidase will prevent or blunt the expected rise in breath hydrogen excretion when a patient with CSID ingests a large sucrose load, and 2) sacrosidase will prevent gastrointestinal symptoms when a patient with CSID ingests a diet containing normal amounts of sucrose.

Patients were evaluated for trial eligibility prior to commencement of the breath hydrogen phase. During the breath hydrogen phase, patients were to undergo three breath hydrogen tests (**BHTs**), which entailed ingesting sucrose (**2g/kg**) followed by placebo, sacrosidase, or **milk/sacrosidase**. During each 3-hour breath test, and for up to 24 hours **thereafter**, gastrointestinal symptoms were to be recorded on a symptom diary. Each breath test was to be separated by one week during which the patient was to maintain a sucrose-free/low starch diet. During the dose-response phase, patients were instructed to maintain a normal sucrose-containing diet while receiving each of four concentrations of sacrosidase (full-strength, **1:10** dilution, **1:100** dilution, **1:1,000** dilution) in random order, for a period of 10 days each. Stool frequency and consistency measures, as well as gastrointestinal symptoms and dietary data, were recorded on a daily basis. Adverse events were collected throughout the trial.

The dosing of the patients was a **14-day** randomized crossover on each of **4** doses (dilutions) of liquid sacrosidase:

Treatment 1:	Full-strength enzyme
Treatment 2:	1:10 dilution
Treatment 3:	1:100 dilution
Treatment 4:	1:1,000 dilution

The dose taken each **time** was:

- **1 mL/meal** for patients weighing no more than 15 kg
- **2 mL/meal** for patients weighing more than **15** kg

The drug was administered orally approximately five minutes after beginning each meal, added to 2-4 ounces of water.

A listing of patients in the safety population who experienced adverse events during the OMC-SUC-2 (S-2) **trial is** presented in Table 8.8.5. All of the events are listed both using the Clinical Investigator's (or parent's) original description as well as the **COSTART** standardized term. The trial phase and dose at the onset of the adverse event and

the resolution of the event (if known) are included in this table. For the purpose of this report, an adverse event was considered to consist of the Clinical Investigator's complete description of an event on a given date, even though such descriptions may have included more than one symptom or observation.

Overall, 26 of the 34 patients in the Trial S-2 safety population experienced at least one adverse event. Most of the adverse events (49/95, 52%) were attributed to concurrent illnesses and were not considered by the Clinical Investigator to be related to sacrosidase. Twelve patients experienced adverse events which were all attributed to concurrent illnesses and were not considered by the Clinical Investigator to be related to sacrosidase. Symptoms associated with these events included abdominal pain, viral infection, strep throat, ear infection, sore throat, fever, malaise, rash, diarrhea, cramping, cough, and runny nose.

Eleven of the 26 patients experienced one or more adverse events that were considered by the Clinical Investigator to be possibly related to sacrosidase. Symptoms associated with these events included abdominal pain, nausea, vomiting, constipation, diarrhea, dehydration, cramps, frequent bowel movements, headache, insomnia, irritability, shock and wheezing. It should be noted, however, that many of these events may have been symptoms of sucrose malabsorption that are typical of patients with CSID and were therefore not unusual for this patient population. Furthermore, most of the patients in the safety population completed both the breath hydrogen phase and the dose-response phase of the trial, suggesting that sacrosidase was well-tolerated by most patients.

TABLE 8.8.5

TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 1 of 10)

Pt Number/ Initials	Adverse Event		Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
	(Original Term)	(COSTART Term)			
02/TG	Vomited	Vomit	During BHT / NI	NI	NI
03/RM	Throwing-up during & after BHT	Vomit	During BHT / Enzyme	NI	Possibly related
	Vomited	Vomit	After BHT / Enzyme	NI	Concurrent illness - not related
	Vomited, not feeling good	Vomit	After BHT / Enzyme	NI	Concurrent illness - not related
06/JR	Started wheezing	Asthma	During BHT / Milk & Enzyme	To ER - ADM. to ICU - dropped from study	Possibly related
08/CB	Has GI bug	Flu Synd	NI / NI	D/R phase delayed	Concurrent illness - not related
11/LA	Nausea	Nausea	NI / NI	NI	NI

BHT = Breath Hydrogen Test Phase

D/R = Dose-Response Phase

NI = Not indicated

NA = Not applicable

TABLE 8.8.5
 TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 2 of 10)

Pt Number/ Initials	Adverse Event (Original Term)	(COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
12/BU	Bottom got very sore	Rash	After BHT / Placebo	NI	NI
	Very irritable	Nervousness	D/R / 1:100	NI	NI
	Very irritable	Nervousness	D/R / 1:100	NI	NI
	Diaper rash	Rash	D/R / 1:10	Rec. topical ointment	Concurrent illness - not related
	Virus, vomited	Infect Virus Vomit	D/R / 1:1,000	NI	NI
13/SM	Has strept throat	Infect Bact	Wk before D/R/NA	Antibiotic	Concurrent illness - not related
	another sore throat with cold	Pharyngitis Rhinitis	Prior to D/R/NA	NI	Concurrent illness - not related
	Flu bug, nausea, vomiting, diarrhea	Flu synd	D/R / 1:1,000	NI	NI
14/ZH	Very irritable	Nervousness	After BHT / Placebo	NI	NI

BHT = Breath Hydrogen Test Phase
 D/R = Dose-Response Phase
 NI = Not indicated
 NA = Not applicable

TABLE 8.8.5
 TRIAL S-2 (OMC-SUC-2) : SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 3 of 10).

Pt Number/ Initials	Adverse Event (Original Term)	(COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
15/PV	Upset stomach, nausea	Dyspepsia	During BHT / Placebo	NI	NI
	Moderate headache	Nausea	After BHT / Placebo	NI	NI
	Weight drop 1.5 lbs,	Headache	Betw. BHT #1	NI	Concurrent illness - not related
	still bruising	Weight Dec	& BHT #2 / NA		
	Weight gain	Ecchymosis	After BHT / Enzyme	NI	NI
	Felt sick, nausea, cramps, freq BM's	Weight Inc	Betw. BHT #2 & BHT #3/NA	NI	Possibly related
.17/SF	Headache	Nausea Pain Abdo Diarrhea Headache	D/R / 1:100	NI	Possibly related
	Irritable for 2 days, diff sleeping for 24 h	Nervousness	After BHT / Enzyme	NI	Possibly related
	Unable to sleep	Insomnia Insomnia	After BHT / Milk & Enzyme	NI	Possibly related

BHT = Breath Hydrogen Test Phase
 D/R = Dose-Response Phase
 NI = Not indicated
 NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2) : SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 4 of 10)

Pt Number/ Initials	Adverse Event (Original Term)	(COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
18/EF	A lot spit out	Saliva Inc	During BHT / Milk & Enzyme	NI	NI
	Ear infection	Infect	Prior to D/R / NA	Antibiotic	NI
	Diarrhea and cramping while on amoxicillin	Diarrhea Pain Abdo	Between BHT & D/R/NA	NI	Concurrent illness - not related
	Thinks that she has tonsillitis (on 4/4/94 reported as "was viral sore throat")	Pharyngitis	D/R/Full strength	NI	Concurrent illness - not related
	Has ear infections	Infect	D/R/Full strength	Antibiotic	Concurrent illness - not related
19/RG	Vomited	Vomit	During BHT / Enzyme	NI	NI
	Ear infection on day 3	Infect	After BHT / Milk & Enzyme	Antibiotic	Concurrent illness - not related
	Flu like symptoms	Flu Synd	After BHT / Milk & Enzyme	NI	NI

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
 TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 5 of 10)

Pt Number/ Initials	Adverse Event (Original Term)	(COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
20/SW	Nausea & vomiting	Nausea Vomit	During BHT / Placebo	NI	NI
	Lots of gagging	Vomit	During BHT / Enzyme	NI	NI
	Fever 103 degrees	Fever	D/R / 1:100	Antibiotic & Tylenol	Concurrent illness - not related
	Fever 101 degrees,	Fever	D/R / 1:100	NI	Concurrent illness - not related
	Strep throat	Infect Bact			
21/KR	Severe lower abdominal pains	Pain Abdo	D/R / 1:100	Saw pediatrician	Possibly related
	Constipation possibly related to enzyme	Constip	D/R / 1:100	NI	Possible related
22/MT	Vomited	Vomit	During BHT / NT	NI	Possible related
	Ear infection	Infect	Betw. BHT #1 & BHT #2 / NA	Antibiotic	Concurrent illness - not related

BHT = Breath Hydrogen Test Phase

D/R = Dose-Response Phase

NI = Not indicated

NA = Not applicable

TABLE 8.0.5
 TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 6 of 10)

Pt Number/ Initials	Adverse Event (Original Term)	(COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
23/RT	Stoma irritated & red	Rash	Betw. BHT #1 & BHT #2 / NA	Use powder/paste PRN	Concurrent illness - not related
	Surgery	React Uneval	Betw. BHT & D/R / NA	Closure of colostomy	Concurrent illness - not related
	Constipation on full dose enzyme	Constip	NI / NI	NI	Possibly related
	Face looked bloated	Edema Face	D/R / 1:100	NI	Possibly related
24/CH	Runny nose, teething,	Rhinitis	Wk. before D/R / NA	Antibiotic	Concurrent illness - not related
	ear infection	React Uneval Infect		(Septra)	
	Vomited after antibiotic after dinner	Vomit	D/R / 1:1,000	NI	Concurrent illness - not related
	Projectile vomiting, skin grey, lips white, went shocky	Shock	D/R / 1:1,000	To E.R. -hold enzyme - gave Pedialyte	Possibly related
	Miserable, screaming	React Uneval	During D/R / NA	D/R phase suspended	NI
Diaper rash	Rash	D/R Phase / full strength	Cleared up in one day	Concurrent illness - not related	

BHT = Breath Hydrogen Test Phase

D/R = Dose-Response Phase

NI = Not indicated

NA = Not applicable

TABLE 8.8.5
 TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 7 of 10)

Pt Number/ Initials	Adverse Event		Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to study Drug
	(Original Term)	(COSTART Term)			
27/JW	Vomited	Vomit	During BHT / Milk & Enzyme	NI	Possibly related
	Earache	Pain Ear	Betw. BHT & D/R / NA	NI	Concurrent illness - not related
	Dehydration	Dehydrat	Betw. BHT & D/R / NA	Adm. to hosp. for rehydration	Possibly related
	Nausea, vomiting, diarrhea	Nausea Vomit Diarrhea	Betw. BHT & D/R / NA	NI	Concurrent illness - not related
	Mass on "R" breast	Neopl Breast	Betw. BHT & D/R / NA	Surgery--benign mass	Concurrent illness - not related
	Dehydration, bilat ear infections, flu-like symptoms	Dehydrat Infect Flu Synd	Betw. BHT & D/R / NA	Adm. to hosp. for rehydration	Concurrent illness - not related
	Bottom sore	Rash	D/R / 1:100	NI	Concurrent illness - not related
	Might be getting a cold	Rhinitis	D/R / 1:10	NI	Concurrent illness - not related

BHT = Breath Hydrogen Test Phase
 D/R = Done-Response Phase
 NX = Not indicated
 NA = Not applicable

TABLE 8.8.5
 TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 8 of 10)

Pt Number/ Initials	Adverse Event (Original Term)	(COSTART Term)	Study Phase/ Tx & Dose	Resolution of Relationship Adverse Event to Study Drug
28/SHW	Abdominal distention	Abdo Enlarge	After BHT / Milk & Enzyme	NI
	Clear runny nose. May have a bug	Rhinitis	D/R / 1:100	NI
	Cough	Cough Inc	D/R / 1:100	NI
	Clear runny nose	Rhinitis	D/R / 1:100	NI
	Fever	Fever	D/R / 1:100	NI
	Runny nose	Rhinitis	D/R / 1:1,000	NI
29/AT	Increased frequency of urine output	Urin Frequency	During BHT / Placebo	NI
31/KF	Vomiting	Vomit	After BHT / Milk & Enzyme	NI
	Symptoms suggestive of URI	Pharyngitis	NI / NI	Antibiotic

BHT = Breath Hydrogen Test Phase
 D/R = Dose-Response Phase
 NI = Not indicated
 NA = Not applicable

TABLE 8.8.5
 TRIAL S-2 (OMC-SUC-2) : SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 9 of 10)

Pt Number/ Initials	Adverse Event (Original Term)	(COSTART Term)	study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to study Drug
32/LD	Nausea/slight abdominal pain - hunger	Nausea Pain Abdo	During BHT / Enzyme	NI	Possibly related
	Large volume of emesis	Vomit	During BHT / Placebo	NI	Concurrent illness - not related
33/LS	No symptoms described	React Uneval	NI / NI	Antibiotics	Concurrent illness - not related
	No symptoms described	React Uneval	NI / NI	Antibiotics	Concurrent illness - not related
34/TB	Stomach ache	Pain Abdo	During BHT / Enzyme	NI	NI
	V. small amount of emesis	Vomit	During BHT / Placebo	NI	Concurrent illness - not related
	Intestinal virus	Infect Virus	D/R / Full strength (1 day) & 1:1,000	NI	Concurrent illness - not related
	Excessive diarrhea and cramping	Diarrhea Pain Abdo	D/R / 1:1,000	Mom suspicious viral in origin	Possibly related

BHT ■ Breath Hydrogen Test Phase
 D/R ■ Dose-Response Phase
 NI ■ Not indicated
 NA ■ Not applicable

TABLE 8.8.5
 TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
 LISTING OF PATIENTS WITH ADVERSE EVENTS

(Page 10 of 10)

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
36/BZ	Abdominal pain, sore throat, general malaise, temperature of 100.9	Pain Abdo Pharyngitis Malaise Fever	After BHT / Placebo	NI	Concurrent illness - not related
37/SK	Notation refers to replacing enzymes "prior to illness"	React Uneval	Betw. BHT & D/R / NA	NI	NI

BHT ■ Breath Hydrogen Test Phase
 D/R ■ Dose-Response Phase
 NI ■ Not indicated
 NA ■ Not applicable

Withdrawals Due to Adverse Events

Patient 6 was the only patient who withdrew from the clinical trial due to an adverse event. The patient started wheezing 90 minutes after receiving sacrosidase treatment and was taken to the emergency room and admitted to the intensive care unit. The patient was subsequently withdrawn from the trial for this event. The wheezing was considered a serious adverse event and is described in more detail below.

Serious Adverse Events

A serious adverse event included any event that was fatal or life-threatening, was permanently disabling, required inpatient hospitalization, or was a congenital anomaly, cancer or overdose. For the purpose of this trial, this definition was extended to events which required an emergency room visit, even if the patient was not admitted to the hospital.

There were no deaths in this trial, but there were four patients who experienced serious adverse events. All of these events were classified as serious because they were associated with **hospitalization** or at least a visit to a hospital emergency room even if the patient was not **admitted**. The four patients who experienced serious adverse events are presented in Table 8.8.6, and **brief** narrative summaries that describe these events for each patient follow.

Patient 6 was a 48-month-old male who was first treated with sacrosidase on **6/16/93**. There were no adverse events reported following this initial treatment. On **6/23/93**, the patient started wheezing 90 minutes after receiving 2 mL of full strength sacrosidase orally during the breath hydrogen phase of the trial. The patient was taken to the emergency room and subsequently admitted to the intensive care unit. He was discharged from the hospital the following day, and was then scheduled to be seen by an allergist. The mother reported that the child had asthma and had been treated with steroids (likely prednisone, but confirmation was not available) for this condition at 5 mg BID, but had been tapered down to 5 mg qd prior to his first dose of sacrosidase on **06/16/93**. The patient's asthma and steroid treatment had not been reported to either the Clinical Investigator or trial coordinator prior to this adverse event. The sacrosidase was discontinued and the patient was withdrawn from the trial because of this event. In the opinion of the Clinical Investigator, this event was possibly related to sacrosidase. The severity of this event was not recorded. The patient was subsequently rechallenged by skin testing with the sacrosidase solution. The allergist reported that the skin test was positive.

Patient 23 was a 6-month-old female who was first treated with sacrosidase on **3/21/94**. On **1/27/94**, the patient's stoma was irritated and red. These symptoms were treated with powder/paste as needed. On **4/7/94**, the patient underwent elective surgery for closure of colostomy. Source documents indicate that the surgery was performed between the breath hydrogen and dose-response phases of this trial. The patient recovered from surgery, completed the trial, and then continued on open-label sacrosidase with meals and snacks. In the opinion of the Investigator, these events were not related to sacrosidase. The severity of each event was not recorded.

Patient 24 was an 8-month-old female who was first treated with **sacrosidase** on **9/7/94**. On **9/20/94**, the patient was started on **Septra®** (sulfamethoxazole and trimethoprim) for otitis media of the left ear; this was the same day the patient started treatment with the **1:1,000** dilution of sacrosidase in the dose-response phase of the trial. The patient vomited immediately after her **Septra®** dose following dinner; the outcome of this event was not available. On **9/22/94**, the patient experienced projectile vomiting, and had gray skin and white lips. She was admitted to the emergency room for these symptoms the same day, and subsequently vomited mucous; her color came back. In addition, "congestion" and "**red ear**" were also reported. Treatment with sacrosidase was interrupted for these events on **9/22/94**, but restarted on **10/11/94**. The patient completed the trial, and continued on open-label sacrosidase with meals and snacks. In the opinion of the Investigator, the vomiting that followed **Septra®** treatment was not related to sacrosidase. The Investigator considered the projectile vomiting, gray skin, and white lips to be possibly related to sacrosidase. The severity of each event was not recorded.

Patient 27 was a **47-month-old** male who was first treated with sacrosidase on **11/15/94**. On **12/19/95**, the patient was dehydrated and admitted to the hospital for re-hydration. The hospital discharge date and the outcome of this event were both not available. On **12/20/95** the patient experienced nausea, vomiting, and diarrhea. The outcomes of these events were not available. The sacrosidase was stopped on **01/17/95** for an unspecified reason following treatment with **milk/sacrosidase**. On **02/02/96**, the patient underwent same-day surgery for removal of a benign mass in his right breast. Following discharge, the patient became dehydrated and was re-admitted to the hospital **for** rehydration. It **was** thought that this episode of dehydration was related to the anesthesia that had been administered for the operation. The outcome of this event was **apparently satisfactory.** Source documents indicate that sacrosidase treatment was re-started on **03/16/96** to begin the dose-response phase of the trial. The

patient completed the trial and was continued on open-label sacrosidase with meals and snacks. In the opinion of the Clinical Investigator, the first episode of dehydration was considered to be possibly related to sacrosidase. The Investigator considered the nausea, vomiting, diarrhea, mass on right breast, and second episode of dehydration (following surgery) to be unrelated to sacrosidase. The severity of each event was not recorded. .

Patients Withdrawn from Controlled Trials

A list of patients who withdrew from each of the two controlled trials after treatment was initiated is given in Tables 8.8.7 and 8.8.8 for Trials S-1 and S-2, respectively. It shows that four patients withdrew from the first trial (S-1) and six from the second trial (S-2). Of these, only one withdrew due to an adverse event. This was patient 6 in Trial S-2.

Table 8.8.7

TRIAL NO. S-1 (OMC-SUC-1): Safety Population
 Listing of Patients Who Withdrew from Study After Treatment*

Patient Number	Treatment Sequence (Breath Hydrogen) ^b	Treatment Sequence (Dose-Response) ^c	Study Phase/Period at Time of Withdrawal	Reason for Withdrawal
3	PE	NI	Dose-Response/2	Lost to Follow-up (Only 2 S&S Diaries Returned)
4	NI	NI	Dose-Response/3	Lost to Follow-up (Only 2 S&S Diaries Returned)
11	PE	NI	Between Breath Hydrogen and Dose-Response	Lost to Follow-up (NO S&S Diaries Returned)
12	PE	NI	Between Breath Hydrogen and Dose-Response	Lost to Follow-up (NO S&S Diaries Returned)

*Received placebo or enzyme.

^bp = Placebo, E = Enzyme; S&S = Stooling and Symptom

NI = Not Indicated

Note: Patient 4 is not in the safety population, but did withdraw from the study.

TABLE 8.8.8

TRIAL NO. S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WHO WITHDREW FROM STUDY
AFTER TREATMENT^a

(Page 1 of 2)

Patient Number	Treatment Sequence (Breath Hydrogen) ^b	Treatment Sequence (Dose- Response) ^c	Study Phase/Period at Time of Withdrawal	Reason for Withdrawal
2	EPM	ADCB	Breath Hydrogen/2	Child had difficulties completing third breath hydrogen test. Difficulties were such that a repeat test was required to obtain accurate test results. Family refused to repeat third breath hydrogen test.
5	UK	BCAD	Breath Hydrogen/1	Discontinued due to symptoms experienced by brother (Patient 6).
6	EPM	CADB	Breath Hydrogen/2	Began wheezing during second breath hydrogen test; study discontinued.
22	UK	CADB	Breath Hydrogen/1	After the informed consent was signed, patient had two placebo BHT's done. Because both tests were negative, the patient was dropped from the study.
29	EPM	DBCA	Breath Hydrogen/3	Mother requested to withdraw due to difficulties encountered getting child to take enzyme solution during the dose-response phase.

^aReceived at least one of the following treatments: placebo, enzyme, milk/enzyme.

^bP = Placebo, E = Enzyme, M = Milk/Enzyme, UK = Unknown.

^cA = Full-strength enzyme, B = 1:10 dilution, C = 1:100 dilution, D = 1:1,000 dilution.

TABLE 8.8.8

TRIAL NO. S-2 (OMC-SUC-2): SAFETY POPULATION
 LISTING OF PATIENTS WHO WITHDREW FROM STUDY
 AFTER TREATMENT^a

(Page 2 of 2)

Patient Number	Treatment Sequence (Breath Hydrogen) ^b	Treatment Sequence (Dose-Response) ^c	Study Phase/Period at Time of Withdrawal	Reason for Withdrawal
16	UK	EACE	Breath Hydrogen/1	Disaccharidase levels provided by the referring physician did not clearly indicate that this patient met study criteria. Because diagnostic BHT's had not been done, it was decided to enroll the patient in the protocol and collect data routinely collected during the week prior to BHT's and schedule the placebo test first. The results of the placebo test were normal, therefore it was determined that the patient did not meet the study criteria. Testing was discontinued.

^aReceived at least one of the following treatments: placebo, enzyme, milk/enzyme.

^bP = Placebo, E = Enzyme, M = Milk/Enzyme, UK = Unknown.

^cA = Full-strength enzyme, B = 1:10 dilution, C = 1:100 dilution, D = 1:1,000 dilution.

Relevant Experimental Data under 16 CFR 1702.9 (b)

Nonclinical Toxicology **Summary for Sacrosidase**

Orphan Medical proposes to use sacrosidase for the treatment of congenital sucrase-isomaltase deficiency (**CSID**) patients. The purpose of this discussion is to provide a summary of the available nonclinical toxicology information on sacrosidase.

An initial review of the literature was undertaken; using the computerized databases of the National Library of Medicine via the **TOXNET** and **TOXLINE** databases. The search used "**sacrosidase**" as a text word; subsequent searches were refined based upon the initial information derived, and may have **keyed** to authors name, specific data types (e.g. mutagenicity, metabolism), etc.

At the request of FDA during a pre-NDA meeting in October 1996 another and more comprehensive literature search was conducted. That search also failed to identify any literature relating to the toxicology of this protein.

A waiver of nonclinical pharmacology tests was requested to the FDA **based** on the following:

1. The enzyme is an exogenous replacement or substitution of a missing endogenous one.
2. There are no appropriate animal models.
3. Efficacy has been clearly demonstrated in humans.

Adsorption, Distribution, **Metabolism** and Excretion

Based on the extensive data base associated with use of this drug in humans, the long-term use of sacrosidase in the baking and confectionery industry and the lack: of toxicity associated with this material **ADME** and **LD50** studies; have not been conducted.

Metabolism of Drug

Because sacrosidase is a large macromolecule, it will not be transported across the gastrointestinal mucosa and into the systemic circulation following oral ingestion. Thus, no systemic toxicity testing directly from the sacrosidase molecule is feasible. Sacrosidase is a naturally occurring enzyme with a glycoprotein structure, it will be digested to **peptides** and eventually amino acids within the small intestine. These metabolic products will be absorbed into the circulation and utilized as nutrients.

Several years of clinical experience with the yeast-derived oral sacrosidase solution in patients as young as **5** months of age have not revealed any evidence of significant toxicity or intolerance.

HUMAN EXPERIMENTAL DATA INVOLVING THE TESTING OF HUMAN SUBJECTS

Orphan Medical Inc., assures the Commission that for all human experimental data submitted with this petition that adequate measures have been taken to ensure against psychological or physical injury to the subjects of the human studies. These studies were conducted in compliance with 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), and meet the criteria under 16 CFR part 1028.

PRODUCT SPECIFICATIONS

Complete quantitative formula for the product

The final dosage form is sacrosidase (8,500 IU/mL) solution composed of a 50%:50% glycerin:water mixture.

Listing of all dosage forms in which the product is available

The final and only dosage form consists of a 118 mL blow-molded, low density polyethylene resin bottle which contains a solution of:

Component:	per mL	per bottle (118 mL):
Sacrosidase solution in 50% glycerin/50% water	8,500 I.U.	1,003,000 I.U.

The dosage of sacrosidase is titrated based on the patient's weight and symptoms-

<u>Amount Taken</u>	<u>Weight</u>
1 mL	<15kg with each meal or snack
2 mL	>15 kg with each meal or snack

Each 1 mL is equivalent to 22 drops of the solution metered through the pierced tip.

PACKAGING SPECIFICATIONS

Name of **manufacturer** of the package
The facility involved in the manufacture of **Sucraid™**
(**sucrosidase**) oral solution is:

NutraMax Products, Inc.
9 **Blackburn** Drive
Gloucester, MA 01930

Specifications for the package

Container/closure

The **drug** product is packaged in a hermetically sealed, 118 mL bottle, formed using blow, fill, seal technology, at the time the product is filled. The bottle has a threaded top and a dropper tip which is compatible with the piercing cap.

Specification: See attached specification

The **cap** is made [REDACTED] and is manufactured by **Unicon** Container Corporation. The cap is placed on the sealed bottle after filling. The cap has a small spike on the inside which can be used to **pierce** the sealed bottle tip at the time of first use.

Specification: See attached specification

Scoop

The scoop is made [REDACTED] which is composed of -
- and is manufactured by **Measurex, S & L** Plastics, **Inc.** It is suitable for food contact use (21 CFR 177.1640). The scoop has no product contact except for measuring the dose.

Specification: See attached specification

Label

The label is manufactured by Labelprint Corporation. The label is constructed of 3.5 **mil** W-treated, flexible, **opaque** white olefin film.

Specification: See attached specification

Complete **packaging** description of carton

The carton is manufactured by Lowell Paper Box, Inc., from 16 point Solid Bleach Sulfate Paperboard line with 0.5 **mil** polyethylene. Its dimensions (upon closing) are **3 1/2 X 1 1/4 X 6 1/8**. The paperboard folding carton for Sucraid (sacrosidase) oral solution holds two bottles and one scoop. The cartons upon receipt must meet manufactures specification for contaminates, color, and defects using **Mil** Standard 105e General Inspection Level I. Defects are defined as critical (**<0.25%**), major (**0.25%**), minor (**2.5%**).

Description of **each** size product offered

Size:	118 mL
Physical Form :	LDPE translucent bottle
Color:	slight yellow
Flavoring:	none added; sweet

LABELING AND PACKAGING SAMPLES

Provided are three **Sucraid** dual pack cartons, containing investigational labeling, and SCOOP.

DRAFT PACKAGE INSERT

Sucraid™ (sacrosidase) oral solution

DESCRIPTION

Sucraid™ (sacrosidase) oral solution is an enzyme replacement therapy for use in the treatment of congenital sucrase-isomaltase deficiency (**CSID**). Each milliliter (**mL**) of Sucraid contains **8,500** International Units (I.U.) of the enzyme **sacrosidase** chemical name **β,D-fructofuranoside** fructohydrolase, which is derived from baker's yeast (*Saccharomyces cerevisiae*). Sucraid also **contains** glycerin (glycerol) in an aqueous solution.

Sucraid is a pale yellow, clear solution with a pleasant sweet taste.- Sacrosidase has an apparent molecular weight of **97 kD**. It is fully soluble with water, milk, fruit juice, and infant formula (DO NOT HEAT).

CLINICAL PHARMACOLOGY

Congenital sucrase-isomaltase deficiency (**CSID**) is a chronic malabsorption disease characterized by an autosomal recessive inheritable disease of sucrase and isomaltase deficiency. **CSID** is characterized by a complete or almost complete lack of endogenous sucrase activity, a marked reduction in isomaltase activity, and a moderate decrease in maltase activity.

Sucrase is a naturally-occurring enzyme that is produced in the **brush** border of the small intestine,, primarily in **the distal** duodenum and jejunum. Sucrase hydrolyzes sucrose, a disaccharide, into its component monosaccharides, glucose and fructose.

In the absence of the endogenous human enzyme, sucrose is not metabolized and is not absorbed by the intestines. The presence of the intact disaccharides in the intestinal lumen leads to the **osmotic** retention of water, resulting in loose stools. Unabsorbed sucrose in the large intestine is fermented by **bacterial** flora to produce hydrogen, methane, and water. These gases generate gastrointestinal discomfort including excessive gas, bloating, abdominal cramps, watery diarrhea, nausea, and vomiting. As a result, undiagnosed **CSID** patients often **fall behind in their** expected growth and development **curves** and fail to thrive. Chronic malabsorption result8 **in** malnutrition.

Measurement of expired breath hydrogen under controlled conditions following a sucrose challenge (a measurement-of excess hydrogen excreted in exhalation) **in** **CSID** patients **have shown** levels as great **as** 6 times **that of normal subjects**. Expert opinion defines clinical **CSID** **as** a condition **having the following features:** **stool pH of less than 6, an increase in breath**

hydrogen of greater than 10 ppm when challenged with sucrose after fasting, and a negative lactose breath test.

Sucraid administered with meals to patients with CSID has been shown in controlled clinical trials to decrease stool frequency and watery diarrhea, improve stool consistency, and decrease abdominal pain, bloating, and gas. In a retrospective study, a number of patients showed improved growth as evidenced by weight for height and weight for age measurements. In addition, sleep disturbances secondary to gastrointestinal symptoms have been alleviated in some patients taking Sucraid. Associated breath hydrogen excretion levels were more indicative of normalized digestion of sucrose.

CSID is often a difficult disease to diagnose. Studies have shown that in pediatric patients with chronic diarrhea of unknown origin that 4-10% had CSID. Because of the difficulties of diagnosing CSID, it may be warranted to conduct a short therapeutic trial (e.g. one week) to assess patient response in those suspected of having CSID.

CLINICAL STUDIES

Clinical trials were conducted to assess the safety and effectiveness of sacrosidase. The first controlled trial was **published** by WR Treem, et al. The second of the controlled trials is in preparation for publication by WR Treem, et al. These publications discuss additional aspects of treating **CSID** patients that may be useful for treating physicians.

INDICATIONS AND USAGE

Sucraid is an oral enzyme replacement therapy indicated for the **treatment** of confirmed **or** suspected congenital sucrase-isomaltase deficiency (CSID) and the prevention of the associated symptoms of sucrose malabsorption such as frequent watery stools, gas, bloating, **abdominal cramping**, explosive diarrhea, and growth retardation.

CONTRAINDICATIONS

Patients known to be hypersensitive to yeast, yeast products, or glycerin (glycerol).

PRECAUTIONS

General: Diabetics should be aware that the use of Sucraid will enable sucrose (and products of its hydrolysis - glucose and fructose) to be absorbed and this must be carefully considered in dietary planning. Although Sucraid provides replacement therapy for the deficient **sucrase** enzyme, it does not provide specific replacement therapy for isomaltase deficiency. Therefore, it may be necessary to continue a restriction in the starch content of the diet in order for patients to optimize diminishment of disease symptoms. The necessity for dietary starch restriction

for patients using Sucraid should be evaluated on a **case** by case basis..

Information for patients: See Patient Package Insert. Patient6 should be instructed to discard bottles of Sucraid **4 weeks** after first opening due to the potential for bacterial growth.

Laboratory **tests:** A positive breath. hydrogen test following oral challenge with sucrose and a negative breath hydrogen test following oral challenge with lactose along with a stool **pH** of less than 6 provides an acceptable diagnosis of CSID. Due to the high incidence of false-negatives in the breath hydrogen test, a therapeutic challenge with Sucraid may be warranted.

The definitive test for diagnosis of CSID has remained the measurement of intestinal disaccharidases following small bowel biopsy.

Prior to the advent of the breath hydrogen test, oral sucrose tolerance tests were utilized for the noninvasive diagnosis of CSID. In children, a rise of blood glucose of **>20 mg/dl** after a 2.0 g/kg sucrose load is considered an indication of sucrose malabsorption. However, there is a high incidence of **false-positive** tests using sucrose **challenge followed** by glucose blood levels due to delayed gastric emptying.

Differential urinary disaccharide testing has been utilized by some physicians for diagnosis of disaccharidase deficiencies. Administration of lactulose, lactose, sucrose, isomaltose, and rhamnose following an overnight fast, with collection of urine for 10 hours and separation of the sugars by thin layer chromatography, has demonstrated excellent **agreement** with small intestinal biopsy for diagnosis of CSID.

In some situations it may be clinically inappropriate/difficult, or inconvenient to perform a small bowel biopsy or breath hydrogen test to make a definitive diagnosis of CSID. In such cases, it is possible that replacement of the suspected deficient sucrase enzyme with Sucraid for three to five days will indicate whether the patient has a deficiency of sucrase. Patients responding to Sucraid with an improvement in clinical symptoms should still be subjected to a diagnostic work-up at a later date so that the diagnosis of primary or secondary **sucrase-isomaltase** deficiency can be made. The effects of Sucraid have not been evaluated **in** patients diagnosed with secondary (acquired) disaccharidase deficiencies:

Drug interactions: There are no known drug-drug **or** drug-food interactions that have been reported with the use of Sucraid.

Carcinogeneais, **mutagenesis**, impairment of fertility: No carcinogenicity, mutagenicity, or fertility studies have been conducted-with Sucraid.

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

Nursing Mothers: The Sucraid enzyme is broken down in the stomach and intestines and the component amino acids and **peptides** are then absorbed **as** nutrients. Use of this product in pregnant or nursing mothers should be evaluated by the treating physician on a case by case **basis**.

Pediatric use: Sucraid has been used in patients as young as 5 months of age. Evidence **from two** controlled trials and one uncontrolled trial in primarily pediatric patients show that Sucraid is safe and effective for the treatment of CSID.

ADVERSE REACTIONS

Adverse experiences with Sucraid in clinical trials were generally minor and were frequently associated with the underlying disease. In clinical studies of up to 54 months duration, physicians treated a total of 52 patients with Sucraid. The **adverse** experiences and respective number of patients **reporting** each event (in parenthesis) were as follows: abdominal pain (4), vomiting (3), nausea (2), diarrhea (2), constipation (2), insomnia (1), headache (1), **nervousness** (1), facial edema (1), and dehydration (1). One asthmatic patient experienced an acute hypersensitivity reaction (wheezing) to Sucraid which resolved with no sequelae. Care should be taken to administer Sucraid for the first time at a facility where acute hypersensitivity reactions can be adequately treated. Alternatively, the patient may be tested for hypersensitivity to Sucraid through skin abrasion testing. Should symptoms of hypersensitivity appear, **discontinue** medication and initiate symptomatic and supportive therapy if indicated.

OVERDOSAGE

No **incidents** of overdose have been reported. Glycerin, a component of Sucraid, is an osmotic diuretic. If an overdose should occur, adequate hydration should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 to 2 mL, or 1 to 2 full measuring scoops (each full measuring scoop equals 1 mL; 22 drops from the bottle tip equals 1 mL) taken orally with each meal or snack diluted with 2 to 4 ounces of water, milk, fruit juice, or infant formula. The beverage or infant formula should be served cold or

at **room** temperature. The beverage or infant formula should not be warmed or heated before or after addition of Sucraid because heating is likely to decrease potency. Clinical **studies** have suggested that a greater portion of the enzyme is delivered to the small intestine if Sucraid is diluted with milk instead of water. This beneficial effect is believed to be due to decreased activity of intragastric pepsin in the presence of milk proteins.

It is recommended that approximately half **of** the dosage be taken at the beginning of each meal or snack, and the remainder be taken at the end of **each meal** or snack.

The recommended dosage is as follows:

- 1 **mL** (one full measuring scoop or 22 drops) per meal or snack for patients up to **15 kg** in body weight. .
- 2 **mL** (two full measuring scoops or 44 drops) per **meal** or snack for patients over **15 kg** in body weight.

Dosage may be administered via the provided 1 **mL** measuring scoop or by drop count method (1 **mL** equals 22 drops from the bottle tip).

HOW SUPPLIED

Sucraid is available in 118 **mL** (4 fluid ounce) translucent plastic bottles, packaged two bottles per box. Each **mL** of solution contains 8,500 International Units (I.U.) of **sucrase** (sacrosidase). Each bottle is supplied with a plastic puncturing cap that is used to open the sealed bottle at first use, and to reseal it after each use. In addition, a 1 **mL** measuring scoop is provided with each bottle. A full measuring scoop is 1 **mL** and the gradation mark indicates one-half (**1/2**) **mL**.

NDC 62161-011-04

Store in a refrigerator at **2° - 8°C (36° - 46°F)**. Discard four weeks after first opening due to the potential for bacterial growth. Protect from heat and light.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:
NutraMax Products, Inc.
Gloucester, MA 01930

Distributed by:
Orphan Medical, Inc.
Minneapolis, MN 55305

For questions of a medical nature, please call Orphan Medical, Inc. toll free at **1-888-BORPHAN** (1-888-867-7426).

DRAFT PATIENT PACKAGE INSERT

Sucraid™
(sacrosidase) oral solution

Please read this leaflet carefully before you **take Sucraid™** (sacrosidase) oral solution or administer Sucraid to a child. **Please** do not throw away this leaflet until you have finished your medicine. You may need to read this leaflet again at a later date. This leaflet **does not** contain all the information on Sucraid. For further information or advice, ask your doctor or pharmacist.

INFORMATION ABOUT YOUR MEDICINE

The name of your medicine is **Sucraid™** (sacrosidase) oral solution. It can be obtained only with a prescription from your doctor.

The purpose of your medicine:

Sucraid is an enzyme replacement therapy for use in the treatment of congenital sucrase-isomaltase deficiency (CSID). CSID is a condition where your body lacks the enzymes needed to properly break down and absorb sucrose (table sugar) and isomaltase (a type of starch) from the intestines.

The symptoms of CSID often include frequent watery diarrhea, abdominal pain, bloating, and gas. In many cases, the symptoms of **CSID** are similar to other medical problems. Only your doctor can make a definite diagnosis of CSID.

Sucraid can help improve the breakdown and absorption of sucrose (table sugar) from the intestine and can help relieve the symptoms of CSID. Sucraid may also possibly improve growth in young children and make it easier to sleep by relieving gastrointestinal symptoms.

Sucraid does not contain the enzyme needed to break down and **absorb** isomaltase (a type of starch) from the intestine. Therefore, you may need to restrict the amount of starch in your diet. Your doctor will tell you if you should restrict **the amount of starch in your diet**.

Discuss **the following** important **information with your** doctor **before you begin to take Sucraid:**

Tell your doctor if you are allergic to, have ever had a reaction to, or have ever had difficulty taking yeast, yeast products, or glycerin (glycerol).

Tell your doctor if you have diabetes. **You** need to be aware that sucrose (table sugar) can **be absorbed** from your diet and your

blood glucose levels may change. Your doctor will tell you if your diet or diabetes medicines need to **be** changed.

Tell your doctor if you **are** nursing **a baby**, are pregnant, or planning to become pregnant.

Side effects to watch for:

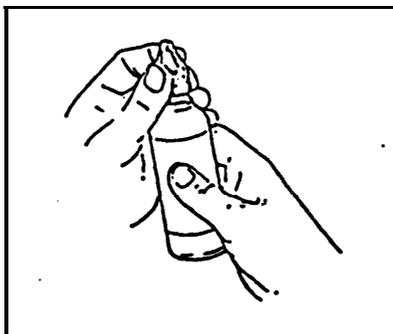
Some patients may experience **a** worsening of abdominal pain, vomiting, nausea, and diarrhea. Constipation, difficulty sleeping, headache, nervousness, and dehydration have also occurred. Other side effects may also occur. **If you notice** these or any other side effects during treatment with Sucraid, check with your doctor.

Stop taking Sucraid and get emergency help immediately **if any** of the following side effects occur: swelling, swelling of the face, or difficulty breathing.

to take your medicine:

Each bottle of Sucraid is supplied with **a** plastic puncturing cap that is used to open the sealed bottle at first use and to reseal it after each use. At first use, tighten the cap until the spike in the cap punctures the bottle tip (see Figure 1). Do not use scissors or a knife to open the sealed bottle. Reseal the bottle after each use by replacing and twisting the cap until tight.

Figure 1. Puncture bottle seal with cap.



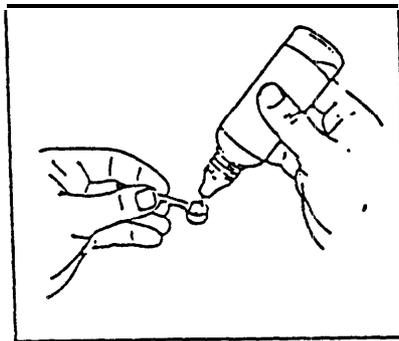
Write down the date the sealed bottle is first opened in the space provided on the bottle label. Always discard the bottle four weeks after first opening it since Sucraid contains no preservatives.

In order to get the full benefits of this medicine, it is very important to take Sucraid as your doctor has prescribed. The

usual dosage is 1 to 2 milliliters (mL) (which equals 1 to 2 full measuring scoops) with each meal or snack.

Measure your dose with the measuring scoop provided (see Figure 2). Do not use a kitchen teaspoon or other measuring device, since it will not measure an accurate dose. A full measuring scoop equals 1 mL and the gradation mark on the inside of the measuring scoop indicates one-half ($\frac{1}{2}$) mL. A 1 mL dose is equal to one full measuring scoop or 22 drops from the bottle tip.

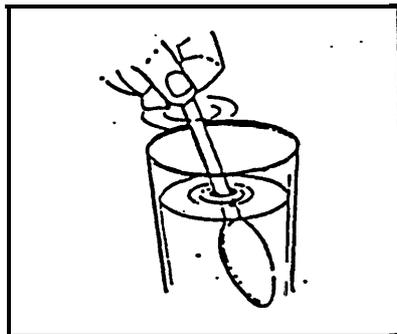
Figure 2. Measure dose with measuring scoop.



Mix your dose in 2 to 4 ounces of water, milk, fruit juice, or infant formula (see Figure 3). Clinical studies have suggested that more of the active ingredient in Sucraid is delivered to the intestine if the dose is mixed in milk instead of water.

NEVER HEAT SUCRAID OR PUT IT IN WARM OR HOT BEVERAGES OR INFANT FORMULA. Heating Sucraid causes it to lose its effectiveness. The beverage or infant formula should be served cold or at room temperature.

Figure 3. Mix dose in beverage-or infant formula.



It is recommended that approximately half of your dosage be taken at the beginning of each **meal** or snack, and the remainder of your dosage be taken at the end of the **meal** or snack.

Storing your medicine:

Sucraid is available in 4 fluid ounce (**118 mL**) translucent plastic bottles, packaged two bottles per box. Each bottle is supplied with a plastic puncturing cap that is used to open the sealed **bottle at** first use and to reseal it after each use. In addition, a **1 mL** measuring scoop is provided with each bottle.

Always store Sucraid in a refrigerator at **36° - 46°F (2° - 8°C)**. Protect. Sucraid from heat and light.

If your bottle of Sucraid has expired (the expiration-date is printed on the bottle label), throw it away.

Keep this medicine in a safe place in your refrigerator where children cannot reach it.

Orphan Medical, Inc.
Minnetonka, Minnesota 55305
Revision Date: April, 1997

MARKETING HISTORY

Sucraid has not been marketed **outside** the United States.

2) JUSTIFICATION BASED UPON PACKAGING NOT BRING PRACTICAL FOR THE SUBSTANCE

Sucraid (sacrosidase) oral solution has been developed **as an** orphan product for the treatment of congenital sucrase isomaltase deficiency (**CSID**). This disease a condition which afflicts up to 0.02% of the **population** of North America, is an autosomal recessive disease of the small intestine characterized by an almost complete **lack** of endogenous sucrase activity. In the absence of sucrase activity, ingested sucrose is not broken down or absorbed in the gastrointestinal (**GI**) tract, **leading to** symptoms of watery diarrhea, abdominal cramps, gas, and bloating. In addition, sucrose malabsorption often leads to decreased weight to height ratios, decreased weight for age, and overall failure to thrive in children with CSID. .

Orphan Medical, Inc. respectfully **requests** an exemption from the Poison Prevention Packaging Act Requirements for Sucraid (sacrosidase) **oral solution** for the following **reasons**:

- there are no alternative drug treatments available for CSID
- the small number of afflicted patients does not make it practical to develop a child-resistant package, (estimated to be 3,000 - **10,000 cases** in the United States)
- the high value associated with quality of life for the population group using the product
- the largest available child-resistant package will not contain the required dosage of Sucraid

EXEMPTION FOR NEW DRUG

As defined in section 201(g)(1) of the Federal Food and Drug Cosmetic **Act (21 U.S.C. 321 (g) (1))**, there have been no adverse reaction reports filed at this time under 21 CFR314.80.

A **New Drug Application, NDA # 20-772**, for **Sucraid** (sacrosidase) oral solution **was** submitted on **May 6, 1997** and-priority review **granted on June 3, 1997**.

Orphan Medical, Inc. understands that under 16 CFR 1702.16 that the Commission is **required to deny** all petitions if the FDA **has** not approved an **NDA**.

As requested by 16 CFR 1702.2, five (5) copies of this petition are enclosed herewith in addition to the original. Three (3) **Sucraid** investigational drug packages have been provided as requested.

All correspondence regarding this petition for exemption to the Poison Prevention Packaging Act should be directed to:

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 475
Minnetonka, MN 55305

Sincerely,



Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
Direct: (612) 513-6969

CC: Melodi McNeil (NDA 20-772)