CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020772

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-772 Submission Date: May 6th, 1997
Sacrosidase Oral Solution
Sucraid™
Orphan Medical Inc.

Reviewer: Lydia C. Kaus
Type of Submission: NDA submission for orphan drug - 1P

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SYNOPSIS:
Sacrosidase is the active ingredient in Sucraid™. It is an enzyme (β-D-fructofuranoside fructohydrolase) derived from bakers yeast, which hydrolyzes sucrose into the monosaccharides, glucose and fructose. The drug is to be used in the treatment of congenital sucrase-isomaltase deficiency (CSID). CSID affects about 0.02% of the population of North America, hence the orphan drug status. It is an autosomal recessive disease of the small intestine, where there can be an almost complete deficiency of endogenous sucrase activity. Symptoms of diarrhoea, abdominal cramps, gas and bloating result from the inability to break down sucrose. CSID children often have deceased weight to height ratios, decreased weight for age and failure to thrive. Present treatment includes adherence to a sucrose-free diet.

The proposed indication for sacrosidase is for treatment of CSID and the prevention of associated symptoms of sucrose malabsorption.

The sponsors have submitted two clinical studies in support of their application (OMC-SUC-1 and OMC-SUC-2).

The proposed final dosage form in this submission is sacrosidase solution in 50% glycerin/50% water containing 8, 500 IU/mL of the active ingredient.

The proposed dose is 1-2 mL diluted with 2 to 4 ounces of water, milk, fruit juice or infant formula, to be taken with each meal or snack with a total dose of 3-10 mL. The individual dose is titrated based on the patient's weight and symptoms:

- 1 mL per meal or snack for patients up to 15 Kg (33 lb) body weight
- 2 mL per meal or snack for patients over 15 Kg (33 lb) body weight

Since Sucraid™ catalyzes the hydrolysis of sucrose, it does not replace isomaltase deficiency, which is also present in CSID.

The sponsors have requested a waiver of human pharmacokinetic and bioavailability studies. Sacrosidase site of action is the small intestine, where it catalyzes the hydrolysis of sucrose to glucose and fructose. It has an apparent M Wt of 97 kD and is not expected to be absorbed

systemically. As a protein it is degraded by proteases to amino acids that are absorbed into the systemic circulation. No drug interactions are anticipated.

FORMULATION:
Sacrosidase solution in 50% glycerin/50%water
8,500 I.U. per ml

PROPOSED DOSE:
The dose is titrated based on the patient's weight and symptoms. Patients are to take 1-2 mL with each meal or snack for a typical daily dosage range between 3-10 mL. Each ml is equivalent to 22 drops of the solution.

Comments:

Labeling:

1. Although the product is titrated according to symptoms, it is rcommended that the sacrosidase solution be given with milk or water to ensure that a solution of pH above 1.5 is used to dilute the product and avoid destruction of the enzyme activity. Giving the product with acidic media such as fruit juice will give a different enzyme activity. The labeling under Dosage and Administration, therefore, should exclude the recommendation of using fruit juice to dilute the product prior to consumption.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation II grants a waiver of evidence to show in vivo bioavailability or bioequivalence.

The basis of this waiver is 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 3) is acting locally within the intestinal tract.

There are two clinical trials to support its safety and efficacy and the sponsors have submitted to the chemistry section information on chemistry, manufacturing and controls of the drug substance and drug product.

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FT initialed
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