CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA NUMBER: 208019
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DIVISION NAME: Division of Cardiovascular and Renal Products
REVIEW COMPLETION DATE: April 27, 2015

DRUG: Potassium Chloride Powder for Oral Solution, 20 mEq
PHARMACOLOGICAL CLASS: Potassium Salts
PROPOSED INVESTIGATIONAL USE: Treatment of patients with hypokalemia with or without metabolic alkalosis; (b) (4) (b) (4)

DOSAGE AND ADMINISTRATION

Dosage is adjusted to the individual needs of each patient. The adult dose for the prevention of hypokalemia is typically 20 mEq/day. Doses of 40-100 mEq/day or more are used for the treatment of potassium depletion. Dosage is divided if more than 20 mEq/day is given such that no more than 20 mEq is given in a single dose. The dose for infants/children, ages (b) (4) to 18 years is 1 - 4 mEq/kg/day, delivered in divided doses, but not to exceed 1 - 2 mEq/kg/dose. Maintenance dosing should not exceed 3 mEq/kg/day (180 mEq/day for a 60-kg person).

DRUG FORMULATION AND COMPOSITION

Composition of Potassium Chloride for Oral Solution, USP, 20 mEq

Component	% w/w	mg/pouch	Function
Potassium Chloride, USP	(b) (4)	1500.00	Active
Colloidal Silicon Dioxide, NF			(b) (4)
Sucralose, NF			
Citric Acid Anhydrous, USP			
Natural and Artificial Orange Flavor			
FD&C Yellow #6			

NONCLINICAL DATA SUBMITTED

None

RELEVANT ISSUE RAISED DURING MIDCYCLE MEETING

Sucralose is one component of the drug Potassium Chloride Powder for Oral Solution, 20 mEq. The sucralose levels in approved drug products are not clear.

REVIEWER'S EVALUATION AND COMMENTS

Excipient sucralose is (b) (4) in one pouch of 20 mEq KCl. Maximum maintenance dose for a (b) (4) human is (b) (4) Thus, the maximum sucralose exposure is (b) (4)

Sucralose is an artificial (non-nutritive) sweetener, is used as drug excipient, and is approved as a food additive, that is, permitted for direct addition to food for human consumption (http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm397725.htm#Sucralose).

FDA CFSAN has determined the 90th percentile Estimated Daily Intake (EDI) for consumers 2 years old and older (''all ages'') to be 98 mg per person per day (mg/p/day), equivalent to approximately 1.6 mg/kg/day. There was a completed battery of toxicity studies to support sucralose as a food additive (http://www.gpo.gov/fdsys/pkg/FR-1998-04-03/pdf/98-8750.pdf). Among the whole battery toxicity studies with sucralose, the only sucralose-related finding is lower body weight in the treated animals:

a. In a combined chronic toxicity/carcinogenicity study (E057), rats were fed diets containing 0, 0.3, 1, or 3% sucralose. Lower body weight gain was observed in all sucralose treated animals in both the carcinogenicity (104 weeks) and chronic toxicity (52 weeks) phases of this study. Mean body weight gain in sucralose-fed rats was 12-25% and 13-26% less than that of the control group at weeks 52 and 104, respectively. No NOAEL was established in this study.

b. In a follow up "Sucralose dietary administration and dietary restriction study in rats (E160)", animals were fed diets containing 0, 1, or 3% sucralose for 26 weeks. "…… FDA determined that reduced food consumption accounted fully for weight gain differences in the 1-percent sucralose-fed group", and concludes that, the less body weight gain attributed to less food consumption in the 1% sucralose-diet group is not an adverse effect, and the 1% sucralose-diet "(equivalent to the 500 mg/kg/day in study E057) is the no observed-effect level for the body weight gain effect observed in sucralose-treated rats in this study".

Using the no-observed-effect level (NOAEL) of 500 mg/kg/day (in rats) and applying a 100-fold safety factor, CFSAN determined an Acceptable Daily Intake (ADI) of 5 mg/kg/day for sucralose.

According to Dr. Banu S Zolnik of Division Of Biopharmaceutics, Office Of Pharmaceutical Quality, total amount of sucralose in the potassium chloride formulation varied during the clinical development:

Experiment 1: sucralose was tested at (b) (4) %). Based on preliminary palatability studies, adjustment for the sucralose amount was needed.

Experiment 2: Sucralose was tested at (b) (4) The conclusion was that in order to increase palatability, reduction in the sucralose amount was required.

Experiment 3: Sucralose was tested at (b) (4) . The conclusion was that appearance and palatability were acceptable for all batches.

Experiment 4: Sucralose at (b) (4) was tested. No observation was reported with respect to palatability.

Comments –

(1) For healthy persons or overweight persons, a modest reduction in food consumption and resulting reduction in body weight may not be an adverse effect. But for patients with chronic health problem under poor nutrition, body weight loss due to "poor palatability"-associated reductions in food consumption is a concern. NOAEL in rats is not established. LOAEL in rats is diet containing 0.3% sucralose, which is ~ 150 mg/kg/day (based on the 500 mg/kg/day for the diet containing 1% sucralose). By applying a factor 10, NOAEL = 15 mg/kg/day.

(2) Human Equivalent Dose for NOAEL is 2.43 mg/kg/day (estimated rat NOAEL of 15 mg/kg/day X 6 [rat km] ÷ 37 [human km]), which is lower than the FDA CFSAN approved ADI of 5 mg/kg/day.

(3) Considering a 100-fold safety factor applied regarding the FDA CFSAN approved ADI of 5 mg/kg/day for sucralose as a food additive, 5 mg/kg/day for sucralose could be the highest limit level for the current NDA 208019.

(4) The sponsor proposed amount of sucralose is (b) (4) pouch (20 mEq KCl). For a 60-kg human, the maximum sucralose exposure of 308 mg/day (5.1 mg/kg/day for a 60-kg individual) slightly exceeds the CFSAN ADI of 5 mg/kg/day.

(5) According Experiment 3 with sucralose at different levels, (b) (4) pack is the lowest sucralose level with acceptable appearance and palatability.

RECOMMENDATIONS

Since the appearance and palatability of the tested potassium chloride batch with sucralose amount of [redacted] (b) (4) was acceptable, and CFSAN-approved sucralose ADI is 5 mg/kg/day (= 300 mg/day for a 60-kg human), final formulation with sucralose [redacted] (b) (4) is acceptable from a pharmacology or toxicology perspective.

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/s/

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04/27/2015

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