Martin J. Hahn
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Re: GRAS Notice No. GRN 000993

Dear Mr. Hahn:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000993. We received the notice that you submitted on behalf of Ausnutria B.V. (Ausnutria) on February 3, 2021 and filed it on May 10, 2021. We received an amendment to the notice on July 19, 2021 that clarified the dietary exposure, analytical data on microbial contaminants and the method used to ensure conformance of the substance to the stated specifications, and details of several toxicological studies.

The subject of the notice is L-carnitine- L-tartrate (LCLT) intended for use as an ingredient in cow or goat milk-based, non-exempt infant formula for term infants at a maximum level of 0.88 mg/100 kcal, providing 0.6 mg L-carnitine/100 kcal. The notice informs us of Ausnutria's view that this use of LCLT is GRAS through scientific procedures.

Our use of the term, "LCLT," in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety did not consult with ONFL regarding the appropriate common or usual name for "LCLT."

Ausnutria describes LCLT as a white crystalline powder that is a salt of L-carnitine and L-tartaric acid. LCLT consists of approximately 68% L-carnitine and 32% L-tartaric acid. Ausnutria provides a description of the manufacturing method for LCLT and states that all materials used in the process are food grade and the methods follow current good manufacturing practices. LCLT is formed by the reaction of L-carnitine and L-tartaric acid in water. The solution is concentrated under vacuum and LCLT is crystallized in ethanol. The wet crystal product is then separated by centrifugation, dried under vacuum, and then sieved to obtain the final LCLT product.

Ausnutria provides specifications for LCLT that include content of L-carnitine (67.2-

69.2% on a dry basis (DB)) and L-tartaric acid (30.8-32.8% DB), specific rotation (-11.0 to -9.5°), pH (3.0-4.5), limits for residue on ignition (≤ 0.2%), loss on drying (≤ 0.5%), arsenic (≤ 1 mg/kg), cadmium (≤ 1 mg/kg), lead (≤ 2 mg/kg), mercury (≤ 0.1 mg/kg), chloride (≤ 0.4%), as well as limits on microorganisms including *Salmonella* (absent in 10 g) and *Cronobacter sakazakii* (absent in 300 g). Ausnutria provides the results of five non-consecutive batch analyses to demonstrate that LCLT can be made to meet the specifications.

Ausnutria provides the results of two stability studies that include a 36-month study and an accelerated six-month study conducted with three batches of LCLT and stored at either 25 °C and 60% relative humidity or 40 °C and 75% relative humidity, respectively. Based on the results, Ausnutria concludes that LCLT was stable for the durations of the studies.

Ausnutria provides estimates of dietary exposure to L-carnitine and L-tartaric acid from the intended use of LCLT in non-exempt infant formula for term infants and from other sources of L-carnitine and L-tartaric acid in infant formula. Ausnutria estimates the dietary exposure to L-carnitine to be 15.5 mg/day (d) (2.54 mg/kg body weight (bw)/d) for infants based on a total L-carnitine level in infant formula (1.29 mg/100 mL), an estimate of the 95th percentile of infant formula consumption (1200 mL/d), and an average body weight of 6.1 kg. Ausnutria estimates the total dietary exposure to L-tartaric acid to be 110.3 mg/d (18.1 mg/kg bw/d) based on an estimate of L-tartaric acid in infant formula (9.19 mg/100 mL) that would result from the intended use of LCLT (0.192 mg/100 mL of L-tartaric acid) and other sources of L-tartrate in infant formula.

Ausnutria states that LCLT dissociates into L-carnitine and L-tartaric acid when dissolved in water during infant formula preparation for consumption. Therefore, Ausnutria discusses published studies on the safety of L-carnitine and L-tartaric acid in lieu of discussing the safety of LCLT.

Ausnutria states that L-carnitine occurs naturally in animal-based foods such as milk and red meat, and L-tartaric acid occurs naturally in fruits. Ausnutria also states that the absorption, distribution, metabolism and excretion of L-carnitine and L-tartaric acid by the human body are well documented in the public literature.

Ausnutria summarizes two 12-week studies in mice, one 13-week and two 1-year studies in rats, and a 13- and a 53-week study in dogs in addition to five studies of reproductive, developmental, and/or teratogenicity studies of L-carnitine and its chloride salt in rats and rabbits. In chronic studies, no adverse effects were reported up to 352 mg/kg bw/d in rats and 200 mg/kg bw/d in dogs. No developmental toxicity was reported up to 100 mg/kg bw/d in rats and 1000 mg/kg bw/d in rabbits, and no reproductive toxicity was seen up to 3000 mg/kg bw/d in rats.

Ausnutria summarizes one 13-week and two 2-year studies in rats, a 150-day study in rabbits, and four developmental toxicity studies in rats, mice, hamsters, and rabbits with tartaric acid or its potassium or sodium salt as the test article. In chronic studies, no adverse effects were reported up to 3,100 (males)/4,100 (females) mg/kg bw/d in

rats and 550 mg/kg bw/d in rabbits. No developmental toxicity was reported up to 274 mg/kg bw/d, 181 mg/kg bw/d, 225 mg/kg bw/d, and 215 mg/kg bw/d in mice, rats, hamster, and rabbits, respectively.

In addition, Ausnutria summarizes the results of an unpublished 90-day dietary study of LCLT in rats in which no adverse effects were reported at 3,934 mg/kg bw/d and 5,042 mg/kg bw/d for male and female rats, respectively, the highest dose levels tested. Ausnutria also discusses the results of two unpublished double-blind randomized and controlled human infant feeding trials that indicated a good safety and tolerability profile of goat milk-based infant formula providing approximately 1.27 and 1.28 mg/kg bw/d LCLT.

Based on the totality of evidence, Ausnutria concludes that LCLT is GRAS for its intended use.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing LCLT bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of the ONFL in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Intended Use in Infant Formulas

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to Ausnutria's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing LCLT to make the submission required by section 412. Infant formulas are the purview of the ONFL in the Center for Food Safety and Applied Nutrition.

Section 301(ll) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of Ausnutria's notice concluding that LCLT is GRAS under its intended conditions of use, we did not consider whether section

301(ll) or any of its exemptions apply to foods containing LCLT. Accordingly, our response should not be construed to be a statement that foods containing LCLT, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Ausnutria provided, as well as other information available to FDA, we have no questions at this time regarding Ausnutria's conclusion that LCLT is GRAS under its intended conditions of use. This letter is not an affirmation that LCLT is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000993 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.10.18 17:46:55 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition