Summary of the dossier: Beta-Hydroxybutyrate salts

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This is an application for authorisation of Beta-Hydroxybutyrate (BHB) salts (sodium, magnesium and calcium) as a novel food in energy/sports bars in the European Union (EU). The application has been compiled in line with the administrative and scientific requirements of Commission Implementing Regulation (EU) 2017/2469 laying down for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. It is also in line with the European Food Safety Authority (EFSA) guidance on the preparation and presentation of an application for authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283.

The three beta-hydroxybutyrate salts which are the subjest of this application are chemically synthesised via a number of chemical synthesis steps. They are intended to be used in energy/sports bars at levels of 26 mg/g (sodium beta hydroxybutyrate), 16 mg/g (magnesium beta hydroxybutyrate) and 27 mg/g (calcium hydroxybutyrate). The production is carried out under strict adherence to the current Good Manufacturing Practices (GMP). The salts are reasonable stable for 24 months. The three synthetic beta hydroxybutyrate salts under this application have no history of safe use in the EU.

Beta-Hydroxybutyrate salts are fatty acid derivatives which are present in milk and milk products. BHB is also produced in the large intestine of animals from fibre via fermentation. Muscles and the central nervous system use BHB for intracellular energy production. After prolonged fasting, the BHB level increases to the level of ketosis. A mild ketosis is the natural adaption of the body to starvation, not to be confused with ketoacidosis e.g. in untreated diabetes. In case of fasting or starvation and the absence of glucose from the diet, the brain will use glucose out of hepatic gluconeogenesis and amino acids from muscle cells. After about a week, metabolism switches to catabolism of fat with subsequent ß-oxidation of fatty acids. BHB is able to pass the blood-brain barrier and feeds into the citrate cycle. It is suspected that increased levels of ketones in turn increase satiety. The salt sodium butyrate DNA transcription is activated by inhibiting HDAC. Stimulated is the transcription of FGF21 (fibroblast growth factor), which promotes fatty acid oxidation, triglyceride clearance and ketogenesis in liver cells.

In animal studies the ingestion of FGF21 lead to an increased energy consumption, decreased blood lipid levels in mice receiving a high fat diet. Despite the diet, there was no insulin resistance and obesity among the mice. Mitochondrial function was increased as well as biogenesis of skeletal muscle and brown fat tissue. BHB is quickly distributed and incorporated into extrahepatic tissue by MCT transporters, which are increasingly expressed in times of fasting/starvation. BHB is subsequently converted to Acetyl-CoA and fed into the citrate cycle. Historically, BHB / ketonic diets were used to treat neurological disorders, such as epilepsy. The cations in the three BHB salts under this application (sodium, magnesium or calcium cations) have know safety and physiological functions.

Safe use of orally administered BHB has been described in infants, and in cancer patients. A ketogenic diet has been used in patients with super-refractory status epilepticus. Adverse effects recorded were metabolic acidosis, hyperlipidemia, constipation, hypoglygemia, hyponatremia and

weight loss. In premature born babies, a ketonic diet was applied and well tolerated. The most common side effects recorded were constipation, hypoglycemia and weight loss. Those side effects were offset by the benefits. High dose intravenous application of sodium BHB was documented in several clinical studies without any side effects. Ketogenic diets resulted in gastrointestinal distress, acidosis, hypoglycaemia, dehydration, lethargy, hyperuricaemia, hyperlipidaemia, kidney stones, easy bruising, decrease in height and weight. When BHB was ingested incorporated in food, no adverse effects were observed.

In toxicity studies, the maximum tolerated intravenous dose for repeated administration was 2000 mg/kg bw/d for rats and dogs. An oral feeding study of BHB in rats showed no toxicological signs, the histophathology and hematology was normal. The consumption of ketone monoesters at 12 and 15.1 g/kg bw/d (male/female) did not cause adverse effects. No mutagenic potential was assessed in vitro or in vivo. Teratogenic toxicity was assessed in rabbits and rats, no effect was found up to 2000 mg/kg bw/d. Theoretical risks include acidosis, sodium and osmotic overloads with respective fluid shifts. Developmental toxicity was tested in rats, there were no specific alterations attributable to the test substance. The use of BHB salts as novel food ingredient and thus its authorization as novel food should therefore be justified.