PUBLIC SUMMARY OF THE DOSSIER

This public summary does not contain confidential information.

Public Summary according to Article 10(2)(a),(b),(e) of Regulation (EU) 2015/2283.

Name and address of the applicant

Chemi S.p.A
Via dei Lavoratori 54
20092 Milano, Italy
www.chemi.com

Name and description of the novel food

Name: L-alpha-glycerylphosphorylcholine (L-alpha-GPC) from soya phospholipids (lecithin).

L-alpha-glycerylphosphorylcholine (L-alpha-GPC) is manufactured from phosphatidylcholine (PC) enriched soya lecithin (i.e., starting material containing about 35% of PC). Chemically the L-alpha-GPC moiety is an integrated part of PC and is one of its metabolites. L-alpha-GPC is to be used as an ingredient in food supplements only, in accordance with Directive 2002/46/EC. It will not replace any other food in the diet but will supplement the regular daily diet. L-alpha-GPC is to be used as a source of choline in food supplements targeted for healthy consumers older than two years of age. The recommended and anticipated daily dose of L-alpha-GPC in food supplements will be 203.7 mg. The form of food supplements will be capsules, each capsule containing 203.7 mg of L-alpha-GPC.

This novel food application contains two L-alpha-GPC ingredients: i) GPC 85% and ii) Alpha Size 100P. GPC 85% is highly viscous, transparent limpid liquid of semi-solid mass containing about 85% of L-alpha-GPC in water. Alpha Size 100P is a white to off-white crystalline powder, highly soluble in water, consisting of 100% L-alpha-GPC. Both products comply with the US Pharmacopeia, National Formulary (USP-NF) Monograph specifications.

Since 2012 in the United States of America (USA), Chemi L-alpha-GPC has been granted a “Generally Recognised as Safe” (GRAS) status (GRN No 419) by the U.S. Food and Drug Administration (US FDA) as a nutrient in conventional beverages and beverage bases, meal replacements, foods and snacks. A solid L-alpha-GPC (Alpha Size 100P) is manufactured and marketed in the USA as dietary supplement in food and beverages. In January 2023, US FDA accepted Chemi L-alpha-GPC as a new dietary ingredient (DNI) for a food supplement use in the USA through FDA’s NDI Notification process (NDIN No 1269).

Production process

The L-alpha-GPC substance manufactured by Chemi is of natural origin in contrast to the same substance that can be chemically synthetised. L-alpha-GPC is obtained by base-catalysed transesterification of PC enriched soya lecithin and subsequent physicochemical purification processes. The starting material to obtain GPC 85% is PC-enriched soya Lecithin. It is a natural mixture of phospholipids, carbohydrates and triglycerides derived from soybean lecithin. PC-enriched soya lecithin is solubilised in methanol and then a de-acylation reaction is carried out in presence of sodium methoxide. On reaction completion, the basic solution is neutralized with sulphuric acid and diluted with methanol. The salts formed are removed by ultra-filtration where the permeate is the rich

solution. The permeate is sent to a reactor for concentration. The fatty acid methyl ester (FAME) phase is separated from the rich lower phase. The rich solution is then decoloured with activated charcoal and filtered. The filtered solution is passed through a basic ionic exchange column to purify L-alpha-GPC. The eluted solution is neutralised using an acetic acid solution before concentration to residue. The residue is dissolved in butanol, the solution is partially concentrated. A mixture of methanol/butanol is added, and the suspension is gradually cooled down to promote the crystallisation. The crystallised product is isolated by centrifugation and washed with butanol. Wet crystallised L-alpha-GPC intermediate is then dissolved in purified water. Residual butanol is removed by azeotropic distillation of the mixture water/butanol. The enriched water solution is further processed to remove ions by treatment with a, ionic exchange resin, decoloured with activated charcoal and ultra-filtered. The ultra-filtered solution is finally concentrated under vacuum until the specified water content is obtained. The final product GPC 85% is then unloaded into high density polyethylene (HDPE) drums.

Alpha Size 100P product is obtained from the "L-alpha-GPC crystallized intermediate" by applying an additional crystallization step with ethanol as follows: The "L-alpha-GPC crystallized" intermediate is dissolved in methanol and the solution is decolored with activated charcoal. After filtration the methanol is removed by distillation. The pasty residue is dissolved with ethanol and crystallized. The wet GPC crystals are isolated by centrifugation and washed with ethanol. The residual ethanol is removed by vacuum drying. The dry intermediate is controlled for compliance with the USP monograph and for residual solvents. The last finishing operation is the delumping (granulation) obtained with a granulator. The finished product is sampled for batch release quality controls.

Butanol is not included Annex I of Directive 2009/32/EC. Therefore, a separate EU-authorisation application for use of butanol in manufacturing of L-alpha-GPC from soya lecithin is under preparation by Chemi S.p.A.

Safety of the novel food

L-alpha-GPC is viewed as harmless since it is a metabolite of PC, one of the main phospholipidic components of soya lecithin (about 19-21%). L-alpha-GPC is also an endogenous substance in humans and is found in human breast milk. It is also present in cow's, goat's and ewe's milk and in the dairy products thereof, and in small amounts also in lecithins of different plants, such as corn, soybean and sunflower. Therefore, it has always been an important integrated part of the human diet to which humans have exposed to.

Following oral exposure, L-alpha-GPC liberates choline which is an essential nutrient for humans. L-alpha-GPC is chemically well characterised and has a body of toxicological and clinical data supporting its safety. The data on rats demonstrated that following oral exposure, L-alpha-GPC is hydrolysed to free choline and glycerol-1-phosphate by phospholipases in the gut. L-alpha-GPC is absorbed rapidly and very completely (90%) in rats appearing in plasma predominantly as free choline. In the two 26-week subchronic studies on L-alpha-GPC in rats and dogs, the adverse effects observed were mild (sedation, reduced food consumption and reduced body weight; the latter ones possibly related to sedation). The adverse effects in dogs and rats were observed only at the highest dose tested. The conducted reproductive/developmental toxicity studies on L-alpha-GPC in rats and rabbits, such as a two-generation reproduction toxicity study in rats, indicated low toxicity to the reproductive/developmental endpoints.

A number of clinical studies have been conducted on L-alpha-GPC. The human clinical studies have tested up to 1,200 mg/person per day of L-alpha-GPC for up to 6 months. Several studies reported no adverse health effects of L-alpha-GPC or mild effects, or overall tolerability was stated to be good. The large number of clinical trials where no or mild adverse health effects were observed led to a

conclusion of safety at the dose of 1,200 mg L-alpha-GPC/person per day. Overall, tolerability to L-alpha-GPC was reported to be good in the conducted human clinical studies.

Furthermore, a safety assessment of the medicine-grade L-alpha-GPC, at the oral dose of 1,200 mg/person per day, reported a 2.1% overall incidence of adverse effects in eight clinical trials including approximately 4,300 subjects, none of which were considered to be “serious.” In addition to central nervous system effects, such as restlessness, insomnia, and headache, issues with the gastrointestinal tract were the most frequently reported effects.

The large number of published and unpublished toxicological and human clinical studies demonstrating the safety of L-alpha-GPC are presented in this Technical Dossier. Since L-alpha-GPC is absorbed as choline, which is biologically active and thus, responsible for the systemic health effects of L-alpha-GPC, it was considered appropriate to base the safety assessment of L-alpha-GPC on the safety of choline. Because human data on L-alpha-GPC and choline after an oral exposure were available, it was also considered more appropriate to base the safety assessment of L-alpha-GPC on the human data rather than the experimental animal data.

Since L-alpha-GPC releases choline, which is an essential nutrient from the diet, it was viewed appropriate to evaluate the health impact of the supplementary exposure to choline from the two Chemi food supplements in order to demonstrate the safety of L-alpha-GPC. Therefore, a cumulative chronic dietary exposure to choline was calculated. The amount of 203.7 mg of L-alpha-GPC accounts for 82.5 mg of choline (i.e. 40.5%). There was no indication that the choline release from L-alpha-GPC at its proposed intake level would exceed the choline Tolerable Upper Intake Levels (ULs) for the different population groups established by the US Institute of Medicine of the National Academies (IOM). Therefore, the exposure to L-alpha-GPC at its proposed use level does not pose a safety concern. This was also in line with the GRAS determination of L-alpha-GPC granted by the US FDA for all consumers older than two years of age.

The available toxicological and human clinical data on L-alpha-GPC did not indicate toxicity at the proposed use level of L-alpha-GPC. The impurities present in the two L-alpha-GPC products do not pose potential risks at the proposed use levels.

Finally, after considerations of the established choline Adequate Intake (AI) levels by European Food Safety Authority (EFSA) and US IOM, together with the safety margins between the cumulative chronic choline dietary exposures and the ULs, it was concluded that the use of L-alpha-GPC, at its proposed use level in food supplements, is most appropriate for the healthy consumers older than two years of age. This is in line with the US FDA accepted age groups.

Overall, the L-alpha-GPC containing products manufactured by Chemi S.p.A, Alpha Size 100P (100% of L-alpha-GPC) and GPC 85% (85% of L-alpha-GPC) are considered safe for their intended uses as food supplements.

Therefore, on the basis of the scientific evidence available, L-alpha-GPC under the conditions of its intended use in food supplements does not pose a safety risk to human health. Nor its intended use mislead the consumer. The labelling of the food supplements will state clearly that the supplement contains “Soya L-alpha-glycerylphosphorylcholine", and it shall bear a statement that the food supplement should not be given to infants and young children under two years of age.