Application for the Approval of Vitalarmor® GF-100, a Basic Whey Protein Isolate, as a Novel Food Ingredient for Use in Infant and Follow-On Formulae, Other Foods for Specific Groups (FSGs), Meal Replacements, and Food Supplements

Pursuant to

Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 Concerning Novel Foods and Novel Food Ingredients

Non-Confidential Summary

Application Submitted by:
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ADMINISTRATIVE DETAILS

Name and Contact Details for Correspondence

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INTRODUCTION

Armor Protéines (Armor) intends to market Vitalarmor® GF 100, a cow's milk-derived basic whey protein isolate, as an ingredient in several foods for specific groups (FSGs), including infant and follow-on formulae, meal replacement beverages (as part of total diet replacement) and dietary foods for special medical purposes, as well as other meal replacements and food supplements. Vitalarmor® GF-100 is obtained from cow's milk using a series of physical separation methods (ion-exchange chromatography and filtration), which are optimised to isolate specifically the minor (basic) whey proteins. Vitalarmor® GF-100 contains not less than 90% total protein. The majority of the protein fraction consists of the basic whey proteins, lactoferrin and lactoperoxidase, which comprise approximately 47 and 26% of Vitalarmor® GF-100, respectively. The remainder of the protein fraction (approximately 20%) is composed of numerous other whey proteins, including other bioactive proteins [*e.g.*, transforming growth factor (TGF)-β_2] that are naturally present in cow's milk.

Vitalarmor® GF-100 may be considered a sub-category of whey, which is already a common ingredient of foods. Thus, beyond their natural occurrence in cow's milk, the protein constituents of Vitalarmor® GF-100 also have a history of safe consumption in the EU as constituents of whey and other ingredients derived thereof already added to food. Several of the cow's milk proteins in Vitalarmor® GF-100 also have related, in some cases, almost chemically identical, counterparts in human milk.

While whey and other protein isolates thereof already are used as food ingredients in Europe, this particular whey protein isolate has not been previously used as an ingredient in foods for the general population in the EU. It is therefore subject to authorisation under Regulation (EC) No 258/97 concerning novel foods and novel food ingredients (European Parliament and the Council of the European Union, 1997) prior to marketing. In accordance with the categories defined by Article 1(2) of Regulation (EC) No 258/97, the basic whey protein isolate is classified under subcategory (e): *"foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating and breeding practices and which have a history of safe food use [in the EU]"*.

An application for the approval of a novel food ingredient under Regulation (EC) No 258/97 is required to follow the European Commission's Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients as prepared by the Scientific Committee for Food (SCF) (97/618/EC; Commission of the European Communities, 1997). Pursuant to the classes of novel foods defined in Section 4 of the SCF's Recommendation ("Scientific Classification of Novel Foods for the Assessment of Wholesomeness"), the basic whey protein isolate belongs to Class 2: "*Complex NF from non-GM sources*", sub-category 1: "*the source of the NF has a history of food use in the Community*".

I SPECIFICATION OF THE NOVEL FOOD

Vitalarmor® GF-100 is characterized by a total protein composition of at least 90%, with lactoferrin and lactoperoxidase combined account for approximately 73% of the ingredient's total composition (47 and 26%, respectively).

The chemical and physical specifications and microbiological specifications for Vitalarmor® GF-100 are presented in Table I-1, along with the analytical methods used to perform the analysis. Since Vitalarmor® GF-100 contains lactoferrin, an iron-binding protein, and lactoperoxidase, a haem-bound protein, a limit for iron content has been included in the specifications. Batch analyses of 5 non-consecutive samples of the final product demonstrate that the established production process produces a consistent product that meets the strict specifications. Therefore, the process can be applied to yield a reproducible product on a commercial scale.

The cow's milk is compliant with the relevant EU hygiene legislation. Analysis of the cow's milk starting material for aflatoxin M_1, lead, and dioxins (dioxin, furan, and PCBs combined) shows conformance with the set limits for raw milk pursuant to Regulation (EC) No 1881/2006 (Commission of the European Communities, 2006). The milk used in the production of Vitalarmor® GF-100 also complies with EU legislation in terms of levels of pesticide residues (EC 396/2005 – European Parliament and the Council of the European Union, 2005) and radioactivity (EURATOM 3954/87 – EURATOM, 1987). Systematic antibiotic survey of the milk is also performed. Milk used as the starting material for Vitalarmor® GF-100 is deemed to be free of bovine tuberculosis.

Vitalarmor® GF-100 is presently packaged in a cardboard box with a double polyethylene liner bag which is food contact-compliant (no migration into the product). When stored at ambient temperature, Vitalarmor® GF-100 is expected to remain stable for up to 36 months as supported by results of stability studies. However, under the present packaging conditions, increases in the moisture content of the product to levels that are outside of the maximum limit for moisture as per the product specifications (*i.e.*, not more than 6%) were apparent after 6 months. Despite the increases in moisture levels, microbial counts remained within the microbiological specification limits at all time points (up to 36 months). For the commercial packaging, Armor intends to use alternative food-contact-compliant packaging material to minimise the moisture increases.

The stability of Vitalarmor® GF-100 is expected to be comparable to the stability of all other whey protein isolates currently available on the market. Denaturation of protein as a result of additional processing of the final food product following addition of Vitalarmor® GF-100 is the only anticipated form of product degradation.

Table I-1 Product Specifications for Vitalarmor® GF-100, a Basic Whey Protein Isolate		
Specification Parameter	**Specification Limit**	**Method of Analysis**
Physical and Chemical Specifications		
Appearance	Yellowish grey powder	Visual Inspection
Foreign matter (Scorched particles)	Absent (Disc B or better[a])	Visual inspection in 25 g (ADMI chart, solubilized with 0.15 M NaCl solution)
pH (5% solution w/v)	5.5 to 7.6	5% (w/v) solution, pH meter
Total Protein	Not less than 90%	Kjeldahl method (IDF20/ISO 8968) [N x 6.38]
Lactoferrin	25 to 75%	HPLC[b]
Lactoperoxidase	10 to 40%	HPLC[b]
TGF-β_2	12 to 18 mg/100 g	ELISA (Quantikine human TGF-β2, R&D Systems)[c]
Moisture	Not more than 6.0%	ISO 5550
Lactose	Not more than 3.0%	Enzymatic method (Lactose/D-Galactose kit, Boehringer Mannheim/R-Biopharm)
Fat	Not more than 4.5%	AFNOR Chimie II 3B 1986
Ash (Residue on Ignition)	Not more than 3.5%	ISO 5545
Iron	≤25 mg/100 g	AAS
Heavy Metals		
Lead	<0.1 mg/kg	ICP-MS
Cadmium	<0.2 mg/kg	ICP-MS
Mercury	<0.6 mg/kg	ICP-MS
Microbiological Specifications		
Aerobic mesophilic count	Not more than 10,000 CFU/g	ISO 4833
Enterobacteriaceae	Not more than 10 CFU/g	ISO 21528-1
Yeasts	Not more than 50 CFU/g	ISO 6611 | IDF 94:2004
Moulds	Not more than 50 CFU/g	ISO 6611 | IDF 94:2004
Escherichia coli	Negative (in 1 gram)	ISO 16649-2
Coagulase positive *Staphylococci*	Negative (in 1 gram)	ISO 6888-3
Salmonella	Negative (in 25 grams)	VIDAS Easy *Salmonella* method (equivalent to ISO6579)
Listeria	Negative (in 25 grams)	VIDAS LIS method (equivalent to ISO 11290-1/A1:2004)
Cronobacter spp.	Negative (in 25 grams)	ISO/TS 22964:2006

AAS = atomic absorption spectrometer; ADMI = American Dry Milk Institute; CFU = Colony Forming Unit; ELISA = enzyme-linked immunosorbent assay; HPLC = High-performance liquid chromatography; ICP-MS = Inductively coupled plasma mass spectrometry; TGF-β_2 = transforming growth factor- beta 2.

[a] American Dry Milk Institute (ADMI) standard discs (Discs A, B, C, or D) representing the following amounts of scorched particles: 7.5, 15.0, 22.5, or 32.5 mg, respectively.

[b] HPLC conducted on in-process samples prior to terminal pasteurisation. To determine levels of each protein in the final product, total protein content is multiplied by % protein in the in-process sample.

II EFFECT OF THE PRODUCTION PROCESS APPLIED TO THE NOVEL FOOD

The production process of the basic whey protein isolate involves physical separation (isolation) of the basic whey proteins from cow's milk (*via* ion exchange chromatography), followed by purification and drying of the isolated basic whey proteins. No chemical processes that would alter any of the constituents that are naturally present in milk are applied during the production process. Apart from an eluting agent and an acidity regulator, no other processing aids are used in the manufacture of the final product. Vitalarmor® GF-100 is manufactured in a facility approved for the manufacture of dairy products. The basic whey protein isolate is produced in accordance with current good manufacturing practices (cGMP) and the principles of Hazard Analysis and Critical Control Points (HACCP) are applied at various stages of the production process.

III HISTORY OF THE ORGANISM USED AS THE SOURCE OF THE NOVEL FOOD

The novel food ingredient is isolated from cow's milk which is ensured to be in compliance with a series of EU legislations that relate to all stages of production, processing, distribution, and placing on the market of cow's milk and products derived thereof.

IX ANTICIPATED INTAKE/EXTENT OF USE OF THE NOVEL FOOD

Vitalarmor® GF-100 is intended for use in the EU as an ingredient in infant and follow-on formulae, meal replacement beverages (as part of total diet replacement), dietary foods for special medical purposes, and food supplements. The proposed uses and use-levels are summarised in Table IX-1 and described in more detail below.

Table IX-1 Proposed Maximum Use Levels for Vitalarmor® GF-100 in Foods for Specific Groups as Defined by Regulation (EU) No 609/2013 (European Parliament and the Council of the European Union, 2013) and Food Supplements in the EU

EU Food Cat.	EU Food Cat.	Food Category Name	Proposed Food-use	Suggested Serving Size	Max. Level per Serving	Proposed Max. Use Level (%)
13	13.1.1	Infant formulae as defined by Regulation (EU) No 609/2013 [1]	Infant Formula	n/a[a]	30 mg/100 g (powder) equivalent to 3.9 mg/100 mL (reconstituted)[b]	0.03 (powder) 0.0039 (reconstituted)
	13.1.2	Follow-on formulae as defined by Regulation (EU) No 609/2013 [1]	Follow-on Formula	n/a[a]	30 mg/100 g (powder) equivalent to 4.2 mg/100 mL (reconstituted)[c]	0.03 (powder) 0.0042 (reconstituted)
	13.2	Dietary foods for special medical purposes defined in Regulation (EU) No 609/2013 [1]	Medical Foods	As specified on a case-by case basis in accordance with Regulation (EU) No 609/2013	Case-by case basis[d]	Case-by case basis[d]
	13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	Meal replacement beverages	250 g	100 mg/meal replacement	0.04
17	17.1	Food supplements as defined in Directive 2002/46/EC[2]	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	--	Up to 610 mg per recommended daily dose	Up to 610 mg per day
	17.2		Food supplements supplied in a liquid form			
	17.3		Food supplements supplied in a syrup-type or chewable form			

EC = European Commission; EU = European Union; n/a = not applicable.
[a] The suggested serving size for infant formula varies according to manufacturer's instructions in line with the baby's age and weight.
[b] Based on 130 g of formula powder/L; [c] Based on 139 g of formula powder/L [d] Case-by case, as recommended by physician, up to 610 mg Vitalarmor® GF-100/day.
References: [1]Commission of the European Communities, 2013; [2]European Parliament and the Council of the European Union, 2002.

Intakes from FSGs (except for Medical Foods)

Intakes in Infants and Toddlers (up to 3 years of age) from Infant and Follow-On Formulae

For use in infant and follow-on formulae, the use-level proposed for Vitalarmor® GF-100 will be adjusted on a case-by-case basis (up to 30 mg/100 g) based on levels of TGF-β_2, a quantitatively minor whey protein identified in Vitalarmor® GF-100, such that following reconstitution, levels of total TGF-β_2 (from Vitalarmor® GF-100 and from normal background occurrence in the base formula) in Vitalarmor® GF-100-supplemented formulae will be comparable to levels of TGF-β_2 in human milk. Considering that TGF-β_2 is present in Vitalarmor® GF-100 at levels of 0.012 to 0.018% (mean 0.015%), TGF-β_2 will occur at levels of up to 3.6 to 5.4 µg per 100 g of formula powder (mean: 4.5 µg per 100 g of formula powder) or 0.47 to 0.70 µg per 100 mL of reconstituted formula (mean: 0.59 µg per 100 mL of reconstituted formula) from the addition of Vitalarmor® GF-100 at the maximum proposed use levels of 30 mg/100 g. In comparison, average TGF-β_2 levels of 0.5 to 5.6 µg/L and maximum TGF-β_2 levels of 57 µg/L were identified in human milk.

Intake estimates of Vitalarmor® GF-100 under the proposed conditions of use in infant and follow-on formulae were generated for 0- to <4-month-old infants, 4- to 6-month-old infants, 7- to 12-month-old infants, 13- to 17-month-old toddlers, 18- to 24-month-old toddlers, and 2- to 3-year-old toddlers. From use in infant and follow-on formulae, the highest intakes were obtained in newborns (up to 4 months of age) (41.3 mg/day or 8.3 mg/kg body weight/day assuming a body weight of 5 kg).

Exposure estimates were also derived for the main protein constituents of Vitalarmor® GF-100, lactoferrin and lactoperoxidase, resulting from the consumption of the ingredient under the proposed conditions of use. The corresponding intakes of lactoferrin and lactoperoxidase from the addition of Vitalarmor® GF-100 to formula in infants up to 4 months of age would be 19.4 and 10.7 mg/day, respectively (equivalent to 3.9 and 2.2 mg/kg body weight/day, respectively, on a body weight basis).

Considering that the use-levels of Vitalarmor® GF-100 for use in infant and follow-on formulae will be adjusted based on total TGF-β_2 content in the final product, and specifically adjustment to levels of TGF-β_2 occurring naturally in human milk, exposure to TGF-β_2 occurring from the possible use of Vitalarmor® GF-100 at the maximum proposed use-level (up to 30 mg/100 g) also was determined. An intake of 41.3 mg Vitalarmor® GF-100 in 0- to 4-month-old infants would result in approximately 7.4 µg TGF-β_2/day or 1.5 µg TGF-β_2/kg body weight/day for a 5-kg baby from Vitalarmor® GF-100. In comparison, exposure from human milk in the range of 0.5 to 5.6 µg/day was estimated, assuming mean concentrations of TGF-β_2 in human milk (0.5 to 5.6 µg TGF-β_2/L). At the highest identified concentration of TGF-β_2 in human milk, exposure would be approximately 57 µg/day.

Intakes in Population Groups 4 Years of Age and Older from Meal Replacement Beverages

With regard to meal replacement beverages, the maximum inclusion level of 100 mg per typical serving (250 g for a standard beverage) is equivalent to 0.04% per product as

consumed. Using national food consumption data (NDNS), highest mean and 95th percentile intakes of 260 and 304 mg/day were estimated in female teenagers and children (4 to 10 years of age), respectively. On a kilogram body weight basis, the highest mean and 95th percentile intake estimates were 3.90 and 13.10 mg/kg body weight/day, respectively, in children (4 to 10 years of age). For comparison, intakes of Vitalarmor® GF-100 from use in meal replacement beverages also were estimated by assuming consumption of 3 beverages per day. Under these conditions, a daily intake of 300 mg of Vitalarmor® GF-100 was derived.

Intakes from Foods for Special Medical Purposes and Food Supplements

In foods for special medical purposes, the inclusion level will also be adjusted on a case-by-case basis based on a physician's recommendations, but such that the maximum intake of Vitalarmor® GF-100 from the consumption of a food for special medical purposes supplemented with Vitalarmor® GF-100 will be not more than 610 mg/day in adults (8.7 mg/kg body weight/day for a 70-kg adult). Similarly, in food supplements intended for adult use, Vitalarmor® GF-100 is intended for inclusion in a manner such that on a daily basis total intakes of Vitalarmor® GF-100 will be up to 610 mg from the recommended use of the food supplement product or 8.7 mg/kg body weight/day for a 70-kg individual. In younger populations (3 years of age and under), Vitalarmor® GF-100 would be added to products such that intakes from daily doses would not exceed 58 mg Vitalarmor® GF-100 or 11.6 mg/kg body weight/day (assuming 5-kg body weight). Additionally, potential combined intakes of Vitalarmor® GF-100 from its use in meal replacement beverages (adults) or formulae (infant and toddlers) and food supplements also were considered. Under this worst-case scenario, Vitalarmor® GF-100 intakes of up to 910 mg/day in adults (13 mg/kg body weight/day for a 70-kg individual) or 100 mg/day in younger groups (20 mg/kg body weight/day for a 5-kg individual) can be anticipated. However, the possibility of exposure to Vitalarmor® GF-100 from the combined consumption of both FSGs (meal replacement beverages in adults and formula in infants and toddlers) and food supplements would be minimized by the proper labelling of food supplements.

Considering the highest estimated level of exposure to Vitalarmor® GF-100 in adults (from its combined use in meal replacement beverages and food supplements), addition of Vitalarmor® GF-100 to foods under the proposed conditions of use would provide up to approximately 428 and 237 mg/day of lactoferrin and lactoperoxidase, respectively (6.1 and 3.4 mg/kg body weight/day, respectively, assuming a body weight of 70 kg). In infants, this would result in worst-case intakes of 47 and 26 mg/day of lactoferrin and lactoperoxidase, respectively (9.4 and 5.2 mg/kg body weight/day, respectively, assuming a body weight of 5 kg).

X INFORMATION FROM PREVIOUS HUMAN EXPOSURE TO THE NOVEL FOOD OR ITS SOURCE

Previous Safety Evaluation and Current Regulatory Status

Vitalarmor® GF-100 is a novel whey protein isolate obtained from cow's milk that is presently not permitted for use as an ingredient in food in the EU; however, in the United States (U.S.), Vitalarmor® GF-100 was determined as Generally Recognized as Safe (GRAS) by a qualified Panel of internationally-recognised Experts in December of 2014 for use in infant and toddler (follow-on) formulae, meal replacement beverages, and medical foods (foods for special medical purposes). Compositionally related whey and whey protein-based ingredients such as demineralised whey and whey protein concentrate are already widely used in food, including in infant and follow-on formulae (Lloyd, 2002; U.S. FDA, 2003a). In the U.S., the Food and Drug Administration (FDA) previously evaluated the safety of whey and whey products and in 1981 issued a final rule affirming the GRAS status of whey and certain modified whey products [reduced lactose whey; reduced minerals whey; and whey protein concentrate (U.S. FDA, 1979, 1981)]. The FDA also has had no questions regarding the more recent determinations of a whey protein isolate (≥90% protein on dry weight basis) (U.S. FDA, 2000) and a bovine milk basic protein fraction[1] [Milk Basic Protein (MBP®)] (U.S. FDA, 2006) as GRAS.

Lactoferrin is one of the main constituent of Vitalarmor® GF-100, present in the isolate at levels ranging from 25 to 75%. The safety of bovine lactoferrin for use in food for human consumption was previously assessed by the European Food Safety Authority (EFSA, 2012a,b). The Panel concluded that bovine lactoferrin was safe for use under the proposed conditions of use. In the EU, bovine lactoferrin is presently permitted for addition to several foods and beverages, including foods for particular nutritional purposes (*i.e.*, medical nutrition and infant nutrition) (European Commission, 2012a,b). In infant and follow-on formulae, lactoferrin is permitted for use at a maximum use level of 100 mg/100 mL. Foods for special medical purposes may provide up to 3,000 mg of lactoferrin per day. Maximum use levels for other conventional food uses range from 50 to 3,000 mg bovine lactoferrin/ 100 g.

Bovine lactoferrin also may be added to a number of foods in other jurisdictions, including in the U.S., where it has been determined to be GRAS for addition to a number of foods including infant formulae (U.S. FDA, 2001a,b, 2003b, 2014a,b). In the U.S., lactoferrin also is marketed as a dietary supplement ingredient, with 250 mg lactoferrin/day identified as the typical dose; however, products containing lactoferrin at levels as high as 1 g/serving are available (PDRNS, 2008; NIH, 2016). Lactoferrin also is permitted for use in infant formulae and conventional foods in several East Asia countries including Japan, China, Korea, and Taiwan.

[1] ≥90 total protein, 40 to 70% lactoferrin, 15 to 60% lactoperoxidase, and ≥0.02% cystatin C, as well as trace amounts of HMG (high-mobility group)-like protein and kininogen fragment 1·2.

Lactoperoxidase appears on the '*List of Existing Food Additives in Japan*' (MHLW, 2014). In the EU, no known permitted uses were identified for lactoperoxidase. In the U.S., lactoperoxidase is currently available for sale as an ingredient of dietary supplements (NIH, 2016). Currently available dietary supplement products appear to provide doses of lactoperoxidase in the 1 to 2 mg/serving range. The safety of a lactoperoxidase-containing system (including thiocyanate and hydrogen peroxide in addition to lactoperoxidase) for use in milk preservation was previously evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1990). However, because the lactoperoxidase system for use in milk does not require addition of exogenous sources of lactoperoxidase, but relies on the natural presence of this enzyme in milk, safety of lactoperoxidase for human consumption from the use of this system in milk was not considered. Food Standards Australia New Zealand also approved the use of a lactoperoxidase-based system as a processing aid (antimicrobial agent) for meat (FSANZ, 2002).

Existing Dietary Exposure

The proteins present in Vitalarmor® GF-100 also are an existing component of the human diet resulting from their presence in cow's milk and cow's milk protein-based ingredients and foods (*e.g.*, dairy products, whey, ingredients derived from whey, and cow's milk protein-based formulae). Lactoferrin and lactoperoxidase are present in cow's milk at concentrations of 100 to 150 mg/L and 30 mg/L, respectively. It is recognised, however, that proteins in cow's milk and cow's milk-based products intended for human consumption will have undergone some denaturation as a result of pasteurisation and other technological processes. While the pasteurisation stage of the Vitalarmor® GF-100 production process will also result in a certain degree of protein denaturation (similar to the level of protein denaturation occurring in cow's milk as a result of pasteurisation), the ingredient will retain in part some level of native proteins. Additional exposure to the native forms of the proteins from the background diet also will occur *via* consumption of raw milk and products made thereof, as well as foods containing whey protein-based ingredients already permitted for use in the EU.

Some formulae currently available on the market are based on cow's milk protein, including whey protein specifically. As such, in formula-fed infants, exposure to the protein constituents of Vitalarmor® GF-100 may also occur *via* consumption of cow's milk protein-based formulae. In comparison to cow's milk protein-based infant formulae already available on the market in which lactoferrin was identified, intakes of lactoferrin from the addition of Vitalarmor® GF-100 to formula would be lower than intakes of lactoferrin from its presence in currently available infant formulae (19.4 *versu*s up to 1,200 mg/day). Although no literature sources were identified for lactoperoxidase concentrations in currently available infant formulae or intakes, according to theoretical estimation, exposure to lactoperoxidase from the addition of Vitalarmor® GF-100 to formula would be lower than intakes of lactoperoxidase from currently available infant formulae (10.7 *versus* approximately 40 mg/day).

The main constituents of Vitalarmor® GF-100, lactoferrin and lactoperoxidase, also occur naturally in human milk. In comparison to the concentrations of each protein in human milk

(up to 3,200 and 0.77 mg/L of lactoferrin and lactoperoxidase in human milk, respectively), concentrations of lactoferrin and lactoperoxidase from Vitalarmor® GF-100, added at the maximum proposed inclusion level, in reconstituted formula will be lower and higher, respectively (approximately 19.4 and 10.7 mg/L of lactoferrin and lactoperoxidase in Vitalarmor® GF-100-containing formula, respectively). Assuming daily consumption of approximately 1,000 mL of human milk by an infant, exposure to lactoferrin from human milk is considerably greater than that which would occur from Vitalarmor® GF-100 as a result of consumption of formula supplemented with the whey protein isolate (up to 640 mg/kg body weight/day *versus* up to 3.9 mg/kg body weight/day). In the case of lactoperoxidase, exposure in infants from human milk would be lower (0.15 mg/kg body weight/day) than that from Vitalarmor® GF-100 added to formula (up to 2.2 mg/kg body weight/day).

TGF-β_2, a quantitatively minor whey protein constituent of Vitalarmor® GF-100, on the basis of which use-levels of Vitalarmor® GF-100 in infant and follow-on formulae will be adjusted such that following reconstitution levels of TGF-β_2 in the formula preparation will be comparable to those in human milk. TGF-β_2 also has been identified in human milk (mean concentrations of TGF-β_2 in mature milk: 0.5 to 5.6 µg/L; up to 57 µg/L), as well as in infant formulae [mean concentration of TGF-β (isoform not specified) in reconstituted formulae: 4.9 µg/L; range: 2.8 to 9.9 µg/L] that are already on the market.

Overall, therefore, significant levels of exposure to the proteins of Vitalarmor® GF-100 are expected as part of the normal diet. During infancy, exposure may occur either *via* consumption of human milk in nursing infants or cow's milk protein-based formula. Apart from exposure *via* direct consumption of cow's milk or products derived thereof, in older population groups, exposure to the whey proteins comprising Vitalarmor® GF-100 also may occur as a result of the consumption of foods which have been supplemented with high-purity proteins or similar whey-derived ingredients and/or dietary supplements intended to specifically provide these proteins.

XI NUTRITIONAL INFORMATION ON THE NOVEL FOOD

Lactoferrin, which accounts for approximately 47% of the composition of Vitalarmor® GF-100, is an 80-kDa transferring family non-haem iron-binding glycoprotein. It is produced in the neutrophils and is found in various secretion fluids. It is one of the main whey proteins found in mammalian milk, with significant amounts present in both human and cow's milk. Lactoferrin has been shown to inhibit certain food-borne pathogens and therefore may be able to reduce incidence of diarrhoea in infants and young children. In infants specifically, it may also participate in the development of the small intestine.

Lactoperoxidase, which contributes approximately 26% of the protein composition of Vitalarmor® GF-100, is an 80-kDa haem-containing glycoprotein with peroxidase activity and is present in human colostrum and other bodily secretions such as saliva and tears. As a component of human milk, lactoperoxidase may contribute to the immune enhancing properties and protective effects of breast milk. Specifically, lactoperoxidase is considered to act as an antibacterial agent, and in the infant specifically, lactoperoxidase may be

involved in the prevention of infections. Lactoperoxidase is also present in cow's milk where it is considered to possess similar biological functions.

Lactoferrin and lactoperoxidase of human and bovine origin are closely related. The amino acid identity between bovine and human lactoferrin has been determined to be at least 69%. Similarly, sequence identity of bovine and human lactoperoxidase has been shown to be 83%.

Vitalarmor® GF-100 also contains proteins that do not contribute significantly to the ingredient's overall composition, but are also known to possess biological activity. TGF-β_2 is one such minor protein constituent that has been identified in Vitalarmor® GF-100. TGF-β_2 is a regulatory cytokine with a multitude of physiological functions that is naturally present in many tissues and organs in the human body. TGF-β_2 also occurs naturally in human milk. The amino acid sequence identity of mature bovine milk-derived TGF-β_2 is 100% in relation to the human counterpart.

Vitalarmor® GF-100 is intended for use in foods, including in infant and follow-on formulae, meal replacement beverages, and foods for special medical purposes, as well as in food supplements as a source of specific cow's milk whey proteins. This could include use of the ingredient as a means of re-introducing specific native whey proteins to a food in which denaturation of the proteins has occurred as a result of processing.

For use in infant and follow-on formulae specifically, Vitalarmor® GF-100 is intended to be used at levels such that following its addition, total TGF-β_2 levels in reconstituted formulae will be comparable to levels of TGF-β_2 in human milk. Since some formulae may be low or deficient (*e.g.*, partially hydrolysed formula) in certain proteins of biological importance such as TGF-β_2, addition of Vitalarmor® GF-100 is consistent with efforts to produce formulae that are compositionally similar to human milk.

Since lactoferrin is an iron-binding protein and lactoperoxidase is a haem-bound protein, these proteins may present an additional source of iron in foods with added Vitalarmor® GF-100. However, the level of iron is limited to ≤25 mg iron/100 g of Vitalarmor® GF-100. Considering worst-case estimates of Vitalarmor® GF-100 intake (combined intakes – see Section IX), this could result in intakes of not more than 20 and 230 µg iron/day in infants up to 4 months of age and adults, respectively. These estimates of iron intakes from Vitalarmor® GF-100 are considerably below the intakes which are considered to be adequate in infants and toddlers (EFSA, 2013) and the daily reference intake in adults (European Parliament and the Council of the European Union, 2011).

XII MICROBIOLOGICAL INFORMATION ON THE NOVEL FOOD

The potential for the presence of micro-organisms in the final product is minimised by including specific control measures at various stages of the manufacturing process that limit the survival and/or carry-over of any potential microbes (see Section II). Furthermore, given the natural source of the ingredient, microbiological specifications also have been

established for Vitalarmor® GF-100. Batch analysis on 5 non-consecutive commercial batches of Vitalarmor® GF-100 confirms that potential micro-organisms are either absent or are found at levels well below the specification limits.

XIII TOXICOLOGICAL INFORMATION ON THE NOVEL FOOD

Absorption, Distribution, Metabolism, and Excretion

Studies examining the metabolic fate of Vitalarmor® GF-100 specifically are not available. However, Vitalarmor® GF-100 is a whey protein isolate consisting primarily of proteins that are naturally present in cow's milk (≥90% protein matter). Therefore, the metabolic fate of the individual constituents present in Vitalarmor® GF-100 is expected to be largely similar as that following their consumption from cow's milk or any other food source containing cow's milk-derived protein (*e.g*., dairy products, powdered milk, whey protein products, *etc*.). Additionally, some limited data were identified related to the metabolic fate and possible bioavailability of the main constituents of Vitalarmor® GF-100, lactoferrin and lactoperoxidase, following oral administration. The data suggest that the protein constituents of Vitalarmor® GF-100 in part withstand digestion in the gastrointestinal tract and to a limited extent, may be absorbed intact.

Toxicological Studies

Safety of the ingredient is primarily supported by the results of toxicological studies conducted with Vitalarmor® GF-100 itself, and is further corroborated by the results of studies with compositionally related products. In order to establish safety, 2 repeat-dose toxicology studies were conducted with Vitalarmor® GF-100. Vitalarmor® GF-100 also was the subject of 2 *in vitro* genotoxicity assays. In a standard subchronic oral toxicity study, groups of weaned Sprague-Dawley rats (main study: 10/sex/group; recovery group: 6/sex/group) were administered Vitalarmor® GF-100 at doses of 0, 600, 1,200, or 2,000 mg/kg body weight by gavage for 13 weeks (followed by 4-week recovery) (Forster *et al*., 2014). While some statistically significant differences were observed between groups of test animals and the controls, none were considered to be related to the administration of the test compound. The highest dose tested in this study, 2,000 mg/kg body weight/day, was determined to be the no-observed-adverse-effect level (NOAEL) for Vitalarmor® GF-100. A further study with juvenile rats (pre-weaning pups) also was performed which was designed to assess safety of the ingredient in an animal population that reflected the target population for the proposed use of Vitalarmor® GF-100 in infant and follow-on formulae (Forster *et al*., 2014). In this study, Vitalarmor® GF-100 was provided *via* gavage to male and female juvenile rats (main study: 10/sex/group; recovery group: 6/sex/group) at a dose of 600 mg/kg body weight/day (only dose tested) starting on Postnatal Day (PND) 7 for a period of 6 weeks (up to PND 49), followed by a 4-week recovery period. As such, test article administration in the juvenile toxicity study commenced with animals still in the neonatal stage of development (PND 7) and continued until approximately the onset of sexual maturation. No biologically significant adverse effects were reported and 600 mg/kg body

weight/day (the only dose level tested) was determined to be the NOAEL for Vitalarmor® GF-100 in juvenile rats. Vitalarmor® GF-100 also was reported to be non-mutagenic when examined in the Ames assay and non-genotoxic when tested in the *in vitro* micronucleus assays (at concentrations of up to 5,000 µg/plate and 2,500 µg/L, respectively) (Forster *et al*., 2014).

In addition to the ingredient-specific studies, several pre-clinical and clinical studies also are available in which the safety of the 2 main constituents of Vitalarmor® GF-100, lactoferrin and lactoperoxidase, and compositionally related ingredients [*e.g*., milk basic protein (MBP®)] was assessed. Toxicity studies conducted with MBP® (54 and 41% lactoferrin and lactoperoxidase, respectively) indicate the material is of low oral acute toxicity, with a medial lethal dose (LD_{50}) in rats of greater than 2,000 mg/kg body weight. No compound-related adverse effects were reported in a 90-day study following oral administration of MBP® to rats at doses of 200 or 2,000 mg/kg body weight/day. A NOAEL of 2,000 mg/kg body weight/day was derived for MBP® in rats on the basis of the 90-day toxicity study. In a 13-week oral toxicity study of a proprietary whey extract (Lactermin®), of which lactoferrin and lactoperoxidase accounted for more than 50% of the total protein content, no adverse effects related to the administration of the extract were reported in rats and a NOAEL of 3,000 mg Lactermin®/kg body weight/day (highest dose level tested) was established. When the potential oral toxicity of bovine lactoferrin was assessed in a number of repeat-dose rat studies, including studies which have previously been reviewed by EFSA, no compound-related adverse effects were reported at doses up to 2,500 mg/kg body weight/day.

There are no data on potential reproductive/developmental effects of Vitalarmor® GF-100. However, the gavage administration of MBP® at a dose of 2,000 mg/kg body weight/day to pregnant female rats on Days 7 through 17 of gestation did not produce any adverse reproductive or developmental effects. A few additional non-standard studies also were conducted with bovine lactoferrin in which parameters related to intrauterine and postnatal rat development were assessed. Administration of lactoferrin at doses of up to 1,300 mg/kg body weight to pregnant dams or up to 2,000 mg lactoferrin/kg body weight/day to pups was not associated with any adverse effects.

Collectively, the available data consistently demonstrate absence of any adverse effects associated with Vitalarmor® GF-100 or its individual main constituents and thus support use of the ingredient under the proposed conditions of use.

Clinical Studies

There were no reported clinical safety studies on Vitalarmor® GF-100. However, numerous published studies were identified in which bovine lactoferrin was provided to infant, child, adolescent, and adult populations. While the studies were primarily designed to assess parameters related to potentially beneficial effects related to the consumption of the protein, some measures of safety also were evaluated. Many of these studies were previously assessed by EFSA as part of their review of the safety of bovine lactoferrin (EFSA, 2012a,b). In addition to the studies that were reviewed by EFSA, a few more recent studies also have

been completed with bovine lactoferrin. Consistent with the earlier results, collectively the studies confirm good tolerability and no adverse effects related to the daily consumption of lactoferrin. Overall, the studies included in EFSA's assessment of lactoferrin safety, as well as the new studies show that oral administration of highly-purified bovine lactoferrin to infants, children, teenagers, and adults at doses exceeding the intakes of lactoferrin expected from the consumption of foods containing Vitalarmor® GF-100 was associated with good tolerability and no adverse effects (doses of up to 2,900 mg in infants, 1,000 mg/day in children, and 7,200 mg in adults). The results of these studies provide corroborative evidence for the safe use of Vitalarmor® GF-100 in humans.

Additionally, no adverse effects were observed in one preliminary open study involving adults with psoriasis and in another double-blind placebo-controlled study with high LDL-cholesterol subjects in which daily doses of 1,000 mg/day (approximately 400 mg of lactoperoxidase and 100 µg of TGF-β_2) and 620 mg/day (approximately 180 mg of lactoferrin, 180 mg of lactoperoxidase, and 93 µg of TGF-β_2) of compositionally related cow's milk-based whey protein isolates, respectively, were provided for 60 days. A few human studies also were identified with MBP® (54 and 41% lactoferrin and lactoperoxidase, respectively). Provided to males for 17 days at a dose of 300 mg (approximately 160 and 120 mg of lactoferrin and lactoperoxidase, respectively) or to females for up to 12 months at a dose of 40 mg (22 and 16 mg of lactoferrin and lactoperoxidase, respectively), MBP® was well-tolerated.

Allergenicity

Considering that the ingredient is derived from cow's milk, the allergenic potential of Vitalarmor® GF-100 was assessed. Neither the main protein constituents of Vitalarmor® GF-100, bovine lactoferrin and bovine lactoperoxidase, nor bovine TGF-β_2, a minor component of the ingredient, are considered major milk allergens; however, consistent with ingredient labelling regulations, any food product containing Vitalarmor® GF-100 will be labelled as containing a "milk protein" ingredient.

Overall Conclusions

Vitalarmor® GF-100 is intended for use as an ingredient in infant and follow-on formulae, other Foods for Specific Groups (FSGs) including meal replacement beverages and dietary foods for special medical purposes, and food supplements.

Under the proposed conditions of use of Vitalarmor® GF-100 in infant formulae and follow-on formulae, maximum exposure is anticipated to occur in infants up to 4 months of age (*i.e.*, 41.3 mg/day or 8.3 mg/kg body weight for a 5-kg baby). Under the proposed conditions of use in meal replacement beverages, the highest mean and 95th percentile intakes of Vitalarmor® GF-100 were determined to be 260 and 304 mg/person/day (in female teenagers and 4- to 10-year-old children, respectively) based on the NDNS. On a body weight basis, 3.9 and 13.1 mg/kg body weight/day (in 4- to 10-year-old children) were identified as the highest mean and 95th percentile intakes, respectively. Assuming a worst-

case scenario of consuming 3 meal replacement beverages per day, an intake of 300 mg of Vitalarmor® GF-100 was estimated. From its proposed use in dietary foods for special medical purposes and food supplements, intakes of Vitalarmor® GF-100 in adults would not exceed 610 mg/day (or 8.7 mg/kg body weight for a 70-kg adult). Use of Vitalarmor® GF-100 in medical foods or dietary supplements intended for younger age groups would provide up to approximately 58 mg of Vitalarmor® GF-100 day (or 11.6 mg/kg body weight for a 5-kg infant). Considering a worst-case scenario of combined Vitalarmor® GF-100 exposure in adults from FSGs (meal replacement beverages) and food supplements, an intake of up to 910 mg/day Vitalarmor® GF-100 was estimated (13 mg/kg body weight for a 70-kg adult). In infants, combined use of formula and food supplement products would result in worst-case Vitalarmor® GF-100 intakes of approximately 100 mg/day or 20 mg/kg body weight/day, assuming a body weight of 5 kg.

Vitalarmor® GF-100 is obtained from cow's milk using only physical separation techniques and as such while the concentration of the individual constituents in the ingredient (*e.g.*, lactoferrin, lactoperoxidase, TGF-β_2) will differ from that in the source material, the production process does not introduce any novel compounds or involve any chemical reactions. Therefore, the individual constituents of the ingredient have a long history of safe consumption from the background diet. Exposure to the protein constituents of the ingredient may occur from the consumption of cow's milk, dairy products, and/or cow's milk protein-based products (*e.g.*, unhydrolysed cow's milk protein infant formula). Furthermore, the main protein constituents of Vitalarmor® GF-100 also are present in human milk. Human milk is also a source of exposure for some of the proteins in the non-lactoferrin/non-lactoperoxidase fraction (*i.e.*, TGF-β_2 is present in human milk). Thus, in infancy, exposure to the proteins of Vitalarmor® GF-100 can also occur through consumption of human milk. The history of safe consumption of the individual protein constituents of the basic whey protein isolate as part of the normal human diet at all stages of life corroborates the safety of Vitalarmor® GF-100.

In addition to history of use, safety of Vitalarmor® GF-100 is primarily supported by the results of toxicological studies conducted with the ingredient, and is further corroborated by the results of pre-clinical and clinical studies with compositionally related products. Two animal studies were performed with Vitalarmor® GF-100: a standard 90-day rat gavage study and a 6-week juvenile rat study conducted to assess safety of the ingredient in an animal population that reflected the target population for the proposed use of Vitalarmor® GF-100 in infant formula. In the 13-week oral gavage study, a NOAEL of 2,000 mg/kg body weight per day, the highest dose tested, was determined for Vitalarmor® GF-100 in Sprague-Dawley rats. In juvenile Sprague-Dawley rats, a NOAEL of 600 mg/kg body weight/day, the only dose tested, was determined for Vitalarmor® GF-100 following 6-week exposure period. The NOAELs are therefore several fold (*i.e.,* 30 to 240 times) greater than the estimates of Vitalarmor® GF-100 intake under the intended conditions of use (8.3 to 20 mg/kg body weight/day for a 5-kg infant and 8.7 to 13 mg/kg body weight for a 70-kg adult).

Further to the ingredient-specific toxicological studies, several pre-clinical and clinical studies on highly-purified lactoferrin, as well as compositionally related ingredients (*e.g.*, other whey extracts/isolates) also were available which further support the safety of Vitalarmor® GF-100.

Collectively, the available data consistently demonstrate absence of any adverse effects associated with Vitalarmor® GF-100 or its individual main constituents and support use of the ingredient under the proposed conditions of use.

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