Initial Assessment

(6S)-5-Methyltetrahydrofolic acid, Glucosamine Salt

Name of Applicant: GNOSIS S.p.A.

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Novel Food Classification: 1.1.

Introduction

An application for the authorisation of (6S)-5-methyltetrahydrofolic acid, glucosamine salt (referred to as "the novel ingredient" hereafter) was submitted to the Food Safety Authority of Ireland (FSAI) by GNOSIS S.p.A. in accordance with *Article 4* of the novel food Regulation (EC) No. 258/97. The application was accepted by the FSAI on July 28th, 2011.

The novel ingredient is chemically synthesised from folic acid and glucosamine hydrochloride and is intended to be used as an alternative source of folate in food supplements in accordance with Directive 2002/46/EC. The novel ingredient falls within the category of "Foods and food ingredients with a new or intentionally modified primary molecular structure", as per *Article 1.2(c*) of the novel food Regulation. The application dossier was prepared pursuant to Commission Recommendation 97/618/EC and in order to assess wholesomeness, the novel ingredient is considered in Class 1.1; "Pure chemicals or simple mixtures from non-GM sources" where the source of the novel ingredient has a history of food use in the Community. The novel ingredient was originally classified in class 1.2 but this was changed to 1.1 in consultation with the applicant.

I. Specification of the novel food

The novel ingredient will be marketed under the trade name of "Quatrefolic". The calcium salt of folic acid is already authorised as a food supplement in the EU while glucosamine hydrochloride has a history of safe consumption as a food supplement prior to the coming into force of the novel food Regulation (EC No 258/97). The glucosamine hydrochloride used to manufacture the novel ingredient is from a non-shellfish source. The specifications of the novel ingredient and its precursors are provided in detail with a final purity of ≥97.5%. The novel ingredient may contain up to 2.5% impurities, mainly folate-related substances resulting from the breakdown or oxidation of methyl-tetrahydrofolic acid. Levels of lead, cadmium and mercury are in

compliance with the maximum levels established in Regulation 629/2008. Analytical data on 3 batches support this compositional information. The novel ingredient is a creamy to light brown powder with 8% or less water content and is deemed to be stable for 12 months at a maximum temperature of 25° C.

II. Effect of the production process applied to the novel food

Production of the novel ingredient involves a series of chemical reactions that begin with the conversion of folic acid to (6S)-5-methyltetrahydrofolic acid in a multistep process. The final phase involves salification of (6S)-5-methyltetrahydrofolic acid with glucosamine hydrochloride to produce the novel ingredient; (6S)-5-methyltetrahydrofolic acid, glucosamine salt. Each stage in the process is controlled and intermediate compounds monitored for purity. The final product is packaged in LDPE bags inside of aluminium compound foil bags and sealed under vacuum.

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III. History of the organism used as the source of the novel food

The novel ingredient is the product of a series of chemical reactions beginning with pure chemicals and therefore this section is not applicable.

IV. – VIII.

There are no GM aspects to this novel ingredient and therefore these sections are not applicable.

IX. Anticipated intake/extent of use of the novel food

The proposed daily intake of the novel ingredient as a component of food supplements is 1.8 mg per person, which is equivalent to 1 mg folate and 0.8 mg glucosamine. A tolerable upper intake level of folate of 1 mg/day for adults has been derived by the Scientific Committee on Food in 2000. The novel ingredient will compete for market share with other folate supplements and so there should be no overall increase in folate intake.

X. Information from previous human exposure to the novel food or its source

Folic acid is naturally present in a variety of foods and is also available on the EU market as the calcium salt of L-5-Methyltetrahydrofolic acid which was authorised as a novel food in the EU in 2008 for use in food supplements (Directive 2002/46/EC). Glucosamine hydrochloride has a history of safe consumption in food supplements prior to 1997 and is not considered a novel ingredient.

XI. Nutritional information on the novel food

Though methyl-tetrahydrofolate and glucosamine are not new to the diet of EU consumers, the combination of (6S)-5-methyl-tetrahydrofolic acid and glucosamine as a single ingredient is considered a novel food within the EU. Just as with the calcium salt, (6S)-5-methyltetrahydrofolic acid, glucosamine salt dissociates completely in an

aqueous environment, including the human stomach, yielding the ionic forms of methyl-tetrahydrofolate and glucosamine. A tolerable upper intake level of folate of 1 mg/day for adults has been derived by the Scientific Committee on Food in 2000. The safety of glucosamine has been evaluated by the EFSA Panel on Dietetic Products, Nutrition and Allergies which considered a daily intake of up to 750 mg glucosamine as safe in 2009. The proposed daily intake of the novel ingredient in food supplements is 1.8 mg per person, which equates to 1 mg folate and 0.8 mg glucosamine, both within the safety limits established by the expert committees. The applicant provided data from a study in human volunteers that demonstrated similar bioavailability for the calcium and glucosamine salts of methyl-tetrahydrofolate.

XII. Microbiological information on the novel food

The novel ingredient is not considered a significant microbiological risk due to the chemical nature of the individual components and production process. However, the microbiological safety of the novel food is supported by batch test results.

XIII. Toxicological information on the novel food

The novel ingredient is greater than 97% pure with any impurities being folate-related products formed during production or as a result of folate degradation. The novel ingredient completely dissociates in the human stomach to its individual components, methyl-tetrahydrofolate and glucosamine whose safe levels are already established. The proposed maximum daily intake of folate from the novel ingredient is 1 mg, while that of glucosamine is 0.8 mg, both within the limits established by expert committees. The safety of the calcium salt of methyl-tetrahydrofolate has already been assessed by EFSA and JECFA and the applicant makes the reasonable argument that because of its similarity to the novel ingredient certain assumptions can be made with regard to safety without the need for extensive toxicological data. Regardless, the applicant provided the results of three *in vitro* genotoxicity tests performed with the novel ingredient that indicated the absence of a genotoxic potential. These results support the applicant's contention that none of the impurities formed during the manufacturing process, including those not detected in the chemical analyses of this novel ingredient, are of toxicological concern. The novel ingredient is not expected to pose an allergenicity risk due to the purity of the starting chemicals and the production process involved, while the starting glucosamine is from a non-shellfish source.

Conclusions

The novel ingredient, (6S)-5-methyltetrahydrofolic acid, glucosamine salt is very similar to the calcium salt of methyl-tetrahydrofolate both from a nutritional and toxicological perspective. Any impurities present in the novel ingredient are identical to those present in the authorised calcium methyl-tetrahydrofolate which has already been assessed. The only compositional variance is that instead of calcium,

glucosamine is present as the counter ion which has a history of safe use in the EU and will not significantly alter consumption levels at the proposed use values.

Recommendation

The Food Safety Authority of Ireland has not identified any safety concerns with the consumption of food supplements containing (6S)-5-methyltetrahydrofolic acid, glucosamine salt at the proposed levels of 1.8 mg/day and therefore considers that this novel ingredient meets the criteria for novel food set out in *Article 3.1.* of the novel food Regulation EC No 258/97.