European Food Safety Authority

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SCIENTIFIC OPINION

Plant stanol esters and blood cholesterol

Scientific substantiation of a health claim related to plant stanol esters and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies

(Question No EFSA-Q-2008-118)

Adopted on 02 October 2008

PANEL MEMBERS

Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren, and Hans Verhagen.

SUMMARY

Following an application from McNeil Nutritionals, submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to "Plant stanol esters and lowering/reducing blood cholesterol and reducing the risk of coronary heart disease".

The scope of the application was proposed to fall under a health claim referring to reduction of a disease risk.

In the context of this application, the term "plant stanol ester" refers to a blend of the plant stanols sitostanol and campestanol, which are obtained from the saturation of plant sterols from food grade plant oils (mainly soybean oil) or tall oil, or blends thereof and esterified with fatty acids from food grade low erucic acid rapeseed oil. The Panel considered that the plant stanol esters for which the health claim is proposed have been sufficiently characterised

Elevated low-density lipoprotein (LDL) blood cholesterol is one recognised risk factor for coronary heart disease (CHD). CHD is an important cause of mortality and morbidity. Lowering LDL-cholesterol by dietary intervention has been shown to reduce the risk of

[1] For citation purposes: Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from McNeil Nutritionals Ltd. related to the scientific substantiation of a health claim on plant stanol esters and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease. *The EFSA Journal* (2008) 825, 1-13.

coronary heart disease. The Panel considers that the claimed effect of lowering LDL-cholesterol is beneficial to human health.

The applicant provided an unpublished meta-analysis comprising 30 randomised, double-blind placebo controlled trials, with generally healthy, normo- and moderately hypercholesterolaemic male and female subjects.

On the basis of the data presented, a clinically significant LDL-cholesterol lowering effect of about 10% can be achieved by a daily intake of plant stanol esters equivalent to 2 g of plant stanols in an appropriate food (e.g. fat-based foods and low-fat foods such as yoghurt), preferably with meals. The size of the cholesterol lowering effect may differ in other food matrices. The Panel concludes that a cause-effect relationship has been established between the intake of plant stanol esters and lowering of LDL-cholesterol, in a dose-dependent manner.

With respect to the association of LDL-cholesterol lowering with reduction in the risk of CHD, the Panel considers that there is evidence that the risk of CHD can be decreased by cholesterol-lowering therapy including dietary intervention strategies. However, there are no studies demonstrating that plant stanol esters have an impact on population-based CHD morbidity and mortality rates.

The Panel considers that products to which plant stanol esters are added should be consumed only by people who need and want to lower their blood cholesterol and that patients on cholesterol-lowering medication should only consume the product under medical supervision.

The Panel considers that the following wording reflects the available scientific evidence: “Plant stanol esters have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of coronary heart disease".

Key words: Plant stanol esters, coronary heart disease, phytosterols, blood cholesterol

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BACKGROUND

Regulation (EC) No 1924/2006[2] harmonises the provisions that relate to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of that Regulation and are authorised in accordance with this Regulation and included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of that Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of that Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, who will make the application and any supplementary information supplied by the applicant available to European Food Safety Authority (EFSA).

Steps taken by EFSA:

- The application was received on 11/02/2008.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction including a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006.
- During the check for completeness[3] of the application, the applicant was requested to provide missing information on 04/04/2008.
- The applicant provided the missing information on 13/05/2008.
- The scientific evaluation procedure started on 15/05/2008.
- During the meeting on 02/10/2008, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to plant stanol esters and "Plant stanol esters and lowering/reducing blood cholesterol and reducing the risk of coronary heart disease".

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: "Plant stanol esters" and "Plant stanol esters and lowering/reducing blood cholesterol and reducing the risk of coronary heart disease".

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of plant stanol esters a positive assessment of its safety, nor a decision on whether

[2] European Parliament and Council (2006). Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

[3] In accordance with EFSA "Scientific and Technical guidance for the Preparation and Presentation of the Application for Authorisation of a Health Claim"

plant stanol esters are, or are not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim and the conditions for use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 17 of Regulation (EC) No 1924/2006.

ACKNOWLEDGEMENTS

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1. Information provided by the applicant

Applicant's name and address: McNeil Nutritionals, a division of Cilag GmbH International; 1 Landis and Gyr Strasse, 6300 Zug; Switzerland

The application includes confidential and proprietary data. The applicant claimed confidentiality and proprietary rights for the information provided in the dossier on specification, batch to batch analysis, manufacturing process, stability information, unpublished trials with plant stanol ester, meta analysis, and data on consumer understanding.

1.1 Food/constituent as stated by the applicant

Plant stanol esters. Trade name: Benecol®

1.2 Health relationship as claimed by the applicant

"Plant stanol esters" are the substance, "blood cholesterol" the risk factor and "coronary heart disease" (CHD) the human disease.

1.3 Wording of the health claim as proposed by the applicant

"By actively lowering/reducing LDL-cholesterol (by up to 14% within 2 weeks, by blocking cholesterol absorption), plant stanol esters reduce the risk of (coronary) heart disease".

1.4 Specific conditions of use as proposed by the applicant

Quantity of food and pattern of consumption required to obtain the claimed effect: Daily consumption of two grams of plant stanols, provided as plant stanol esters, preferably with meals. Use as part of a balanced and varied diet and combined with a healthy lifestyle. Food products with added plant stanol esters labelled with the proposed health claim would comply with mandatory labelling requirements of the Commission Regulation (EC) No 608/2004.

1.5 Similar claims as proposed/authorized by other entities

The Netherlands Nutrition Centre (Stalenhoef *et al*., 2001), the Ministry of the Health, Labour and Welfare Japan (2002), the US Food and Drug Administration (FDA 2003; FDA 2006) and the Swedish Nutrition Foundation (2006a, 2006b) have already approved health claims for plant stanol esters which are similar to those proposed in this application. However, two of the claims only state that plant stanol esters *may* reduce the risk for CHD, and the other two solely claim the decrease of blood LDL-cholesterol without any claim regarding reduction of risk for CHD.

The applicant also lists various international and national organisations which endorse the consumption of 2 g-3 g/day of plant stanols to lower blood LDL-cholesterol: The Joint British Societies' Guidelines (JBS, 2005), the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III, 2002) and the American Heart Association (Smith *et al*., 2006). Other organisations also endorse the consumption of plant stanols without giving a dose recommendation: the World Health Organization (WHO, 2002a), the Finnish Internal Medicine Society (2004) and the Australian Heart Foundation (2007).

2. Assessment

2.1 Characterisation of the food/constituent

Plant stanols occur naturally in free and esterified form in only small amounts in the daily diet. They can be industrially produced from vegetable oil sterols (vegetable sterols) and from tall oil sterols (wood sterols). Plant stanols are produced from the saturation of plant sterols (e.g. sitosterol and campesterol) to plant stanols (e.g. sitostanol and campestanol). Plant stanol esters are the products derived from the esterification of plant stanols with fatty acids.

The main plant stanols in a plant stanol blend are sitostanol and campestanol. Plant stanols produced from tall oil sterols, sourced in Scandinavia, contain approximately 94% sitostanol and approximately 6% campestanol. A blend of plant stanols obtained from typical commercial soybean oil based plant sterol contains 68–75% sitostanol and 25 – 32% campestanol.

In the context of this application, the term "plant stanol ester" refers to a blend of the plant stanols sitostanol and campestanol. These are obtained from the saturation of plant sterols from food grade plant oils (mainly soybean oil) or tall oil, or blends thereof and esterified with fatty acids from food grade low erucic acid rapeseed oil. Batch to batch analysis of 10 consecutive factory scale batches provided by the applicant indicated a mean of 82.3% sitostanol (SD=1.9) and of 17.7% campestanol (SD=1.9) of total stanols. According to the specification provided by the applicant, the final plant stanol esters product (Benecol® Classic produced by Raisio Benecol Ltd.) consists of at least 55 weight% of stanols and approximately 40 weight% rapeseed oil fatty acids, max. 3 weight% of free sterols, max. 0.1 weight% free fatty acids and max. 0.1 weight% moisture.

Throughout this opinion, quantities of stanol esters are expressed as the equivalent weights of free [i.e. un-esterified] stanols.

The Panel concludes that the plant stanol esters for which the health claim is proposed have been sufficiently characterised.

2.2 Relevance of the claimed effect to human health

Coronary heart disease (CHD) is a leading cause of mortality and morbidity in European populations with over 1.9 million deaths in the European Union and over 4.35 million deaths in Europe each year (Pedersen *et al*., 2005). Elevated blood cholesterol is an important modifiable risk factor in the development of CHD (WHO, 2002b).

It has been shown that blood cholesterol can be decreased by drugs and by dietary and lifestyle changes (Denke, 2005; Gordon, 2000; Katan, *et al*., 2003; Law, 2000; Ornish *et al*., 1998; van Horn *et al*., 2008). The Panel considers that the claimed effect of lowering LDL-cholesterol is beneficial to human health.

2.3 Scientific substantiation of the claimed effect

The review of the human data made by the applicant was considered as comprehensive. Pertinent data have been identified and included in the application.

LDL-cholesterol lowering effect

The applicant provided an unpublished meta-analysis comprising 30 randomised, double blind placebo controlled trials. Most of them were published in peer reviewed scientific journals and

considered pertinent to substantiating the ability of plant stanol esters to lower LDL-cholesterol. The meta-analysis included normo- and moderately hypercholesterolaemic male and female subjects. The administered doses of plant stanol esters ranged from 0.8 to 4 g per day (expressed as free stanols). Thirteen of these studies used 2 g per day, and 2 studies 4 g per day. The duration of the studies varied from 2 to 52 weeks, 21 studies lasted 4-8 weeks. In 16 of the studies, margarine type spreads were used as vehicle to administer the plant stanol esters preparations. Other vehicles used were yoghurt (5 studies), mayonnaise (2 studies), gel capsules (2 studies), butter, low fat cheese, milk, muesli, "ready-made low fat meals", pasta (each 1 study).

The blood LDL-cholesterol lowering effect varied by the experimental settings. It ranged from 3 to 14% compared to the placebo control groups with an average LDL-cholesterol decrease of 0.36 mmol/L (14 mg/dL). Taking into account only the treatment groups in which the stanol esters dose was equivalent to 2 g stanols per day or more, the average LDL decrease was about 10% for both genders (95% CI 9-12%) or 0,37 mmol/L (14.4 mg/dl).

A 9-week trial with 0.83 g plant stanol esters per day administered in margarine indicated a need to consume more than 1 g plant stanol esters per day to achieve any significant decrease of blood LDL-cholesterol levels (Miettinen and Vanhanen, 1994). Based on the meta-analysis and the studies provided by the applicant, a dose-response relationship was observed up to 4 g stanols per day. The response however, substantially flattens at doses higher than about 2.3-2.5 g per day and seems to level off at doses towards 4 g per day (Cater *et al*., 2005; Hallikainen *et al*., 2000).

Some studies included in the meta-analysis did not indicate the manufacturer of the plant stanol preparation. However, all studies indicated sitostanol and campestanol as the compounds of the tested preparation. The ratio between sitostanol and campestanol in the tested preparation varied among the studies. In most studies, this ratio was however similar or within the range given in the specification for Benecol® Classic (Raisio Benecol Ltd.). In order to demonstrate that the sitostanol/campestanol ratio does not have a relevant impact, the applicant provided data from two intervention studies, one with a moderately hypercholesteraemic population and the second study with a non-hypercholesterolemic population. The intervention groups received vegetable oil- and wood-based stanol ester mixtures with considerably different sitostanol/campestanol ratios. The results of both studies showed that all administered plant stanol preparations had similar or equivalent LDL-cholesterol lowering effects, irrespective of the sitostanol/campestanol ratio of the preparation (Gylling and Miettinen, 1999; Plat and Mensink, 2000). It was further demonstrated that the blood LDL-cholesterol lowering effect of plant stanol esters preparations was consistent and of a similar magnitude, irrespective of whether plant stanols had been esterified with fatty acids from butter or vegetable oil (Gylling and Miettinen, 1999).

Regarding administration regimens, the difference in the LDL-cholesterol lowering effect of 2.5 g per day plant stanol either ingested as a single dose or divided in 3 doses over a day, seems to be negligible. The LDL-cholesterol lowering effect for a single dose was 9.5% and the value for the divided dose was 10.2% (Plat *et al*., 2000). In a study with low-fat yoghurt or milk used as the vehicle, the LDL-cholesterol lowering effect appeared to be more pronounced when the study product was ingested with meals compared to between meals (Seppo *et al*., 2007).

The effect of plant stanol esters on blood LDL-cholesterol is usually established within the first two weeks and remains stable over the intake period and HDL-cholesterol is not influenced in a significant way (Miettinen *et al*., 1995; Hallikainen and Uusitupa, 1999). The so-called North Karelian plant stanol esters trial involved 153 moderately hypercholesterolaemic subjects receiving a margarine type spread with or without 2.6 g plant stanol esters per day over 12

months. The blood LDL-cholesterol lowering effect of about 15% compared to the placebo group could be sustained over the full intervention period. After ceasing consumption of plant stanol esters margarine the blood cholesterol levels returned to baseline. This study indicates that plant stanol esters consumption must be continued to retain the blood LDL-cholesterol lowering effect (Miettinen *et al*., 1995).

The LDL-cholesterol lowering effect of plant stanol esters added to margarine-type spreads, mayonnaise and yoghurt was consistent and of similar magnitude among the studies. Similar results were also obtained for butter, low fat cheese, "ready-made low fat meals" and for pasta, each of them used as the vehicle in a single study (Gylling and Miettinen, 1999; Jauhiainen *et al*., 2006; Salo and Wester, 2005). Some studies suggested that the LDL-cholesterol lowering effect might be smaller when stanol esters were administered in soft gel capsules, milk and muesli, compared to margarine-type spreads (Lagstroem *et al*., 2006; Seppo *et al*., 2007; Theuwissen and Mensink, 2007; Woodgate *et al*., 2006). Overall, the provided studies indicated that the fat content of the vehicles does not have a significant impact on the LDL-cholesterol lowering efficacy, but other matrix effects might have an impact.

The Panel concludes that a cause-effect relationship has been established between the intake of plant stanol esters equivalent to 1-4 g of stanols per day in a dose-dependent manner, added to an appropriate food (e.g. plant stanol esters added to fat-based foods and low-fat foods such as yoghurt), and the lowering of LDL-cholesterol. A significant LDL-cholesterol lowering effect of about 10% can be achieved by a daily intake of plant stanol esters equivalent to 2 g of plant stanols in an appropriate food such as margarine-type spreads, yoghurt and mayonnaise, preferably with meals. The size of the cholesterol-lowering effect may differ according to the food matrix.

LDL-cholesterol and coronary heart disease

The relationship between serum LDL-cholesterol levels and coronary heart disease (CHD) has been intensively studied and both epidemiological studies and randomised controlled clinical trials have indicated a causal relationship between elevated LDL-cholesterol and CHD (Mensink *et al*., 2003; Stamler *et al*, 1986; Verschuren *et al*, 1995). Furthermore, there is evidence that the risk of CHD is reduced by cholesterol-lowering therapy (Pedersen *et al*., 2005), including dietary intervention strategies (Denke, 2005; Ornish *et al*., 1998; van Horn *et al*., 2008). However, there are no human intervention studies demonstrating that plant stanols reduce the risk of coronary heart disease.

The applicant justified the lack of animal studies in the dossier by referring to the quality of the available human data.

2.4 Panel's comments on the proposed wording

Taking into account the scientific evidence presented, the Panel considers that the following wording reflects the scientific evidence:

""Plant stanol esters" have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of (coronary) heart disease".

2.5 Conditions and restrictions of use

The Panel recommends that the products to which plant stanol esters are added should be consumed only by people who want to lower their blood cholesterol.

With respect to the specified conditions of use, it is suggested that the labelling provisions outlined in Commission Regulation (EC) No 608/2004 shall continue to apply for products making the proposed reduction of disease risk claim.

The scientific justification of the claim is related to a daily intake of plant stanol esters equivalent to 2 g of plant stanols added to fat-based foods and low-fat foods such as yoghurt. Other food forms should be evaluated for their cholesterol-lowering effect.

The product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years. Patients on cholesterol lowering medication should only consume products with added plant stanol esters under medical supervision.

Relevant studies performed under free living conditions showed the feasibility of consuming the recommended level of plant stanol esters added to food (2 g per day). The panel considers that the amount of plant stanol esters needed to lower blood LDL-cholesterol and the pattern of consumption can reasonably be achieved through consumption of foods with added plant stanol esters as part of a balanced diet.

CONCLUSIONS AND RECOMMENDATIONS

On the basis of the data presented, the Panel concludes that:

- Plant stanol esters for which the health claim is proposed have been sufficiently characterised.
- Elevated blood LDL-cholesterol is one risk factor for coronary heart disease. Coronary heart disease is an important cause of mortality and morbidity. Lowering LDL-cholesterol by dietary intervention has been shown to reduce the risk of coronary heart disease.
- A cause-effect relationship has been established between the consumption of plant stanol esters and lowering of LDL-cholesterol, in a dose-dependent manner.
- A clinically significant LDL-cholesterol lowering effect of about 10% can be achieved by daily intake of 2 g of plant stanols in an appropriate food (fat-based foods and low-fat foods such as yoghurt), preferably with meals. The size of the cholesterol lowering effect may differ in other food matrices.
- There are no human intervention studies demonstrating that plant stanol esters reduce the risk of coronary heart disease.
- The recommended amount of plant stanol esters required to lower blood LDL-cholesterol and patterns of consumption can reasonably be achieved as part of a balanced diet.
- The Panel recommends that the products to which plant stanol esters are added should be only consumed by people who want to lower their blood cholesterol.
- The Panel considers that the following wording reflects the available scientific evidence: *"Plant stanol esters have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of coronary heart disease."*
- With respect to the specified conditions of use, it is suggested that the labelling provisions outlined in Commission Regulation (EC) No 608/2004 shall continue to apply for products bearing the proposed reduction of disease risk claim.

DOCUMENTATION PROVIDED TO EFSA

Plant stanol esters. February 2008. Submitted by McNeil Nutritionals. (EFSA serial No: 0038_UK).

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