EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013. Scientific Opinion on the substantiation of a health claim related to the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast ric e, sugar - cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d - - tocopheryl hydrogen succinate , riboflavin and inositol hexanicotinate in Limicol ® and reduction of blood LDL - cholesterol concentrations pursuant to Article 14 of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and reduction of blood LDL-cholesterol concentrations pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Laboratoire Lescuyer, submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and reduction of blood LDL-cholesterol concentrations. The Panel considers that the food which is the subject of the claim is sufficiently characterised. The Panel considers that reduction of blood LDL-cholesterol concentrations is a beneficial physiological effect. High LDL-cholesterol is a risk factor in the development of coronary heart disease. In weighing the evidence, the Panel took into account that, although no evidence was provided for an LDL-cholesterol lowering effect of any of the single food constituents in Limicol® at the proposed conditions of use or as to how the ingredients individually or in any combination could contribute to the claimed effect and despite the lack of a dose-response relationship observed in one human intervention study, three human intervention studies conducted by two independent research groups showed an effect of the combination of food ingredients in Limicol® on blood LDL-cholesterol concentrations. The Panel concludes that a cause and effect relationship has been established between the consumption of the combination of artichoke leaf dry extract standardised in

[1] On request from the Competent Authority of France following an application by Laboratoire Lescuyer, Question No EFSA-Q-2012-00968, adopted on 12 July 2013.

[2] Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific opinion.

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caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and a reduction in blood LDL-cholesterol concentrations.

KEY WORDS

Artichoke, monacolin K, OPC, garlic, vitamins, cholesterol, health claims

SUMMARY

Following an application from Laboratoire Lescuyer, submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and reduction of blood LDL-cholesterol concentrations.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction. The application includes a request for the protection of proprietary data.

The food that is the subject of the health claim is Limicol®. The Panel considers that the food, the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol®, which is the subject of the health claim, is sufficiently characterised.

The claimed effect proposed by the applicant is "oral consumption of the food supplement Limicol® significantly reduces circulating low-density lipoprotein-cholesterol (LDL-cholesterol) level, thus reducing the risk of coronary heart disease". The target population proposed by the applicant is "males and females from 18 to 65 years with mild to moderate hypercholesterolaemia". The Panel considers that reduction of blood LDL-cholesterol concentrations is a beneficial physiological effect. High LDL-cholesterol is a risk factor in the development of coronary heart disease.

The applicant provided as pertinent to the claim three published human intervention studies together with the full study reports.

The Panel notes that the three human intervention studies, which were conducted by two independent research groups showed an effect of the combination of 600 mg artichoke leaf dry extract with 30-36 mg caffeoylquinic acids, 500 mg red yeast rice with 2 mg monacolin K, 10 mg sugar-cane derived policosanols, 20 mg French maritime pine bark extract with 18 mg OPC, 30 mg garlic dry extract with 0.25 mg allicin, 30 mg α-tocopherol equivalents, 5 mg riboflavin and 9 mg inositol hexanicotinate in Limicol® on LDL-cholesterol concentrations when consumed daily in three doses with the major meals. The Panel also notes that doubling the dose of the food that is the subject of the health claim did not have an additional effect on LDL-cholesterol concentrations.

The applicant claims that monacolins in red yeast rice, sugar cane-derived policosanols and the artichoke leaf extract are the food constituents in Limicol® which are responsible for the claimed effect. The Panel notes the well established role of monacolin K at doses of 10 mg per day in lowering LDL-cholesterol. However, the Panel also notes that the available evidence does not establish that any of the other food constituents in Limicol®, including policosanols and artichoke leaf extract, exert an LDL-cholesterol lowering effect in humans on their own and that at the proposed conditions of use no evidence has been provided for an LDL-cholesterol lowering effect of any of the food constituents in Limicol®, or as to how the ingredients individually or in any combination could contribute to the claimed effect.

In weighing the evidence, the Panel took into account that although no evidence was provided for an LDL-cholesterol lowering effect of any of the single food constituents in Limicol® at the proposed conditions of use or as to how the ingredients individually or in any combination could contribute to the claimed effect, and despite the lack of a dose-response relationship observed in one human intervention study, three human intervention studies conducted by two independent research groups showed an effect of the combination of artichoke leaf dry extract standardised in caffeoylquinic acids,

monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® on blood LDL-cholesterol concentrations.

The Panel concludes that a cause and effect relationship has been established between the consumption of the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and a reduction in blood LDL-cholesterol concentrations.

The Panel considers that the following wording reflects the scientific evidence: "A combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate reduces blood LDL-cholesterol concentrations. High LDL-cholesterol is a risk factor in the development of coronary heart disease."

The Panel considers that in order to bear the claim a product should provide 600 mg artichoke leaf dry extract with 30-36 mg caffeoylquinic acids, 500 mg red yeast rice with 2 mg monacolin K, 10 mg sugar-cane derived policosanols, 20 mg French maritime pine bark extract with 18 mg OPC, 30 mg garlic dry extract with 0.25 mg allicin, 30 mg α-tocopherol equivalents, 5 mg riboflavin and 9 mg inositol hexanicotinate in three daily doses to be consumed with the major meals. The target population is adults in the general population wishing to reduce their blood cholesterol concentrations.

In relation to restrictions of use, the Panel refers to the Summary of Product Characteristics of lovastatin-containing medicinal products available on the EU market.

The Panel also refers to the opinion by the EFSA CONTAM Panel on citrinin, a nephrotoxic mycotoxin which can be produced by some strains of *Monascus purpureus*.

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BACKGROUND

Regulation (EC) No 1924/2006[4] 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 this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of this 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 this Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 22/11/2012.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction. The application includes a request for the protection of proprietary data.
- On 19/12/2012, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 30/01/2013, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 04/02/2013.
- On 27/02/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 04/03/2013 and restarted on 02/05/2013, in compliance with Article 16(1) of Regulation (EC) No 1924/2006.
- On 02/05/2013, EFSA received the requested information.
- During its meeting on 12/07/2012, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and reduction of blood LDL-cholesterol concentrations.

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: the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and reduction of blood LDL-cholesterol concentrations.

[4] 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. OJ L 404, 30.12.2006, p. 9–25.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of a combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate, a positive assessment of its safety, nor a decision on whether a combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate is, or is 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 of 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.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Laboratoire Lescuyer, ZAC de Belle Aire Nord, 15 rue le Corbusier, 17440 Aytré, France.

The application includes a request for the protection of proprietary data (Morange et al., 2011, unpublished; Barrat et al., 2012; Barrat et al., 2012, unpublished-a; Barrat et al., 2012, unpublished-b; Laboratoire Lescuyer, 2012, unpublished; Zaïr et al., 2012, unpublished-a; Zaïr et al., 2012, unpublished-b; Barrat et al., 2013; Ogier et al., 2013).

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is Limicol®, a food supplement that contains a combination of: red yeast rice (0.4 % monacolins), sugar cane-derived policosanols (90 % policosanols, 60 % octacosanol) and artichoke leaf extract (5-6 % caffeoylquinic acid). This food supplement also contains as other minor constituents pine bark extract (90 % procyanidolic oligomers), garlic extract (0.8 % allicin, 1.8 % alliin), vitamin E, riboflavin (vitamin B2) and inositol hexanicotinate (vitamin B3).

Health relationship as claimed by the applicant

According to the applicant, oral consumption of the food supplement Limicol® significantly reduces circulating low-density lipoprotein-cholesterol level, thus reducing the risk of coronary heart disease.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Limicol® has been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease."

Specific conditions of use as proposed by the applicant

The applicant has proposed as conditions of use a daily intake of three tablets over a four-week period. The target population proposed by the applicant is males and females from 18 to 65 years with mild to moderate hypercholesterolaemia.

ASSESSMENT

1. Characterisation of the food/constituent

The food that is the subject of the health claim is Limicol®.

Limicol® is a food supplement which contains per tablet 200 mg of artichoke leaf dry aqueous extract standardised in caffeoylquinic acids (5-6 %), 167 mg red yeast rice (produced by fermentation of rice with the fungus *Monascus purpureus*, approx. 0.4 % monacolin K in hydroxyacid and lactone form (also known as lovastatin)), 3.7 mg sugar-cane extract (90 % policosanols of which 60 % octacosanols), 6.7 mg French maritime pine bark extract (90 % procyanidolic oligomers (OPC); plant:extract ratio: 1000:1), 10 mg garlic dry extract standardised in allicin (0.8 %), 10 mg α-tocopherol equivalents, 1.6 mg riboflavin and 2.9 mg inositol hexanicotinate.

At the proposed conditions of use (3 tablets/day), Limicol® provides around 600 mg artichoke leaf dry extract with 30-36 mg caffeoylquinic acids, 500 mg red yeast rice with 2 mg monacolin K, 10 mg

sugar-cane derived policosanols, 20 mg French maritime pine bark extract with 18 mg OPC, 30 mg garlic dry extract with 0.25 mg allicin, 30 mg α-tocopherol equivalents, 5 mg riboflavin and 9 mg inositol hexanicotinate.

Information pertaining to batch-to-batch variability and stability has been provided.

Caffeoylquinic acids, monacolin K, policosanols, OPC, allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate can be measured in foods by established methods.

The Panel considers that the food, the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol®, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is "significantly reduces circulating low-density lipoprotein-cholesterol (LDL-cholesterol) level, thus reducing the risk of coronary heart disease". The target population proposed by the applicant is "males and females from 18 to 65 years with mild to moderate hypercholesterolaemia".

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 (Petersen et al., 2005). Elevated blood cholesterol is an important modifiable risk factor in the development of CHD (WHO, 2002).

It has been shown that blood cholesterol can be decreased by drugs, and by dietary and lifestyle changes (Ornish et al., 1998; Gordon, 2000; Law, 2000; Katan et al., 2003; Denke, 2005; Pedersen et al., 2005; Van Horn et al., 2008).

The Panel considers that reduction of blood LDL-cholesterol concentrations is a beneficial physiological effect. High LDL-cholesterol is a risk factor in the development of CHD.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Pubmed, Science Direct, Wiley Interscience and Google Scholar using the following terms: ([Limicol] OR ([red yeast rice] OR [monascus] OR [monacolin] OR [cholestin] OR [Zhi Tai] OR [hong qu] OR [red koji] OR [red rice] OR [Xue Zhi Kang]) AND ([artichoke] OR [Cynara scolymus]) AND ([Sugar cane] OR [Saccharum officinarum] OR [policosanol] OR [octacosanol])) AND ([cholesterol] OR [LDL-cholesterol]). Inclusion criteria comprised studies carried out with the combination of ingredients which is the subject of the claim in healthy subjects or subjects with untreated mild to moderate hypercholesterolaemia, and with blood total or LDL-cholesterol concentrations as the primary outcome.

Through the literature search, the applicant identified one published randomised controlled trial (RCT) (Ogier et al., 2013, claimed as proprietary) and provided summary reports of two, at the time of the application, unpublished, randomised controlled trials (Barrat et al., 2012, unpublished-a; Barrat et al., 2012, unpublished-b, both claimed as proprietary). Upon a request from EFSA, the applicant also provided the full study reports (Morange et al., 2011, unpublished; Zaïr et al., 2012, unpublished-a; Zaïr et al., 2012, unpublished-b) of the above mentioned studies. The results of the studies by Barrat et al. (2012, unpublished-a) and Barrat et al. (2012, unpublished-b) were published (Barrat et al., 2012; Barrat et al., 2013) after the application had been submitted to EFSA.

All three RCTs identified as pertinent by the applicant investigated the effect of the combination of ingredients in Limicol® on blood LDL-cholesterol concentrations compared to placebo (dicalcium phosphate, microcrystalline cellulose, maltodextrin, calcium citrate, tricalcium phosphate, beet powder and magnesium stearate). In all studies, exclusion criteria excluded subjects using blood lipid lowering medication, women on oestrogen replacement therapy or taking oestrogen-containing contraceptives, and subjects with BMI <18.1-18.5 or ≥27.5-28 kg/m^2, or any diseases which could affect blood lipid concentrations. In all but one study (Ogier et al., 2013), subjects were aged between 18-65 years and had plasma LDL-cholesterol concentrations between 3.36 and 5.69 mmol/L at baseline. Subjects in the study by Ogier et al. (2013) were between 18 and 55 years old, and had plasma total cholesterol concentrations >5.68 mmol/L at baseline. In all studies, compliance was assessed by returned pill boxes at every study visit and study subjects were encouraged not to change their dietary habits or their physical activity levels throughout the study. Power calculations were performed in two of the studies presented (Barrat et al., 2012; Barrat et al., 2013).

In a double-blind, placebo-controlled parallel study (Ogier et al., 2013), 39 subjects (28 women) were block randomised to consume three times daily one tablet of either Limicol® (n=19) or placebo (n=20) with the major meals for 16 weeks. The primary outcome was the change from baseline in LDL-cholesterol concentrations at week 16. Blood lipids were measured at baseline and at weeks 4, 8, 12 and 16. Physical activity and body weight were not assessed in this study. Three-day dietary records were completed by subjects at baseline and before each visit. Two subjects dropped out in each group (reasons not reported). Apart from the analysis presented in the publication, the applicant also presented an analysis using a mixed model (SAS PROC MIXED) assuming a compound symmetry covariance structure. In the baseline-adjusted intention-to-treat (ITT) analysis a significant treatment per time interaction (p=0.038) was observed with respect to plasma LDL-cholesterol concentrations (baseline adjusted mean difference at week 16: -0.71 mmol/L 95 % CI: -1.03 to -0.39 mmol/L, p<0.0001). The correlation between changes in saturated fatty acid (SFA) intake and changes in LDL-cholesterol concentrations was weak. Therefore, including these variables in the model did not add any information to the analysis. The Panel notes that reasons for drop-outs were not reported and that no information on the imputation/handling of missing data was provided, but also that the number of drop-outs was small. The Panel considers that this study shows an effect of the combination of ingredients in Limicol® on blood LDL-cholesterol concentrations.

In a double-blind, placebo-controlled parallel study (Barrat et al., 2012), 45 subjects (31 women) were block randomised to consume three times daily two tablets of Limicol® (n=15), one tablet of Limicol® plus one placebo tablet (n=15), or two placebo tablets (n=15) with the major meals for four weeks, followed by a four-week observational period with no intervention. The primary analysis of the study was the difference in plasma LDL-cholesterol concentrations between the six tablet group and placebo at week 4. Blood lipids were measured at baseline and at week 4, and at the end of the follow-up period. Dietary intake and physical activity were examined at baseline and week 4. All subjects completed the study. Apart from the analysis presented in the publication, the applicant provided an analysis using a mixed model (SAS PROC MIXED) assuming a compound symmetry covariance structure. This analysis also included the follow-up period. In the baseline-adjusted ITT analysis, a significant treatment per time interaction (p=0.013) was observed among the three groups. Pair-wise comparisons at week 4 adjusted for multiple comparisons by the Tukey-Kramer method were statistically significant for both the six tablet and the three tablet groups vs. placebo (baseline adjusted mean differences: -0.53 mmol/L, 95 % CI -1.02 to -0.05 mmol/L, p=0.03 and -0.62 mmol/L, 95 % CI -1.1 to -0.14 mmol/L, p=0.0097, respectively). The correlations between changes in SFA intake, body weight and physical activity levels and changes in LDL-cholesterol concentrations were weak. Therefore, including these variables in the model did not add any information to the analysis. At the end of the follow-up period (without intervention) LDL-cholesterol concentrations in the intervention groups returned towards baseline values. Differences in LDL-cholesterol concentrations between the intervention groups and the placebo group were no longer significant (baseline adjusted mean differences: 0.25 mmol/L, 95 %CI -0.26 to 0.75 mmol/L and -0.05 mmol/L 95 %CI -0.54 to 0.42 mmol/L for the six and the three tablet group, respectively). The Panel considers that this study shows

an effect of the combination of ingredients in Limicol® on blood LDL-cholesterol concentrations. However, the Panel notes that no dose-response relationship was observed in the study.

In a double-blind, placebo-controlled parallel study (Barrat et al., 2013), 100 subjects (70 women) were randomised to consume three times daily one tablet of either Limicol® (n=50) or placebo (n=50) with the major meals for 16 weeks. The primary analysis of the study was the difference in blood LDL-cholesterol concentrations between groups at week 16. Blood lipids were measured at baseline and at weeks 4, 10 and 16. Physical activity and dietary intakes were assessed at baseline and before the final visit. One subject, through illness, did not complete the study and the missing values were replaced by carrying forward the last observation. The applicant also presented an analysis using a mixed model (SAS PROC MIXED) assuming a compound symmetry covariance structure. In the baseline-adjusted ITT analysis, no significant treatment per time interaction (p=0.912) but a significant main effect of treatment was observed with respect to plasma LDL-cholesterol concentrations (baseline adjusted mean difference: -0.57 mmol/L 95 % CI -0.76 to -0.38 mmol/L, p<0.0001). The Panel interprets this finding as meaning that the main effect of treatment took place during the first observation period (four weeks). This interpretation is in line with the results of the ANCOVA analyses at time points 4 and 16 which adjusting for baseline showed a significant difference in blood LDL-cholesterol concentrations between groups at week 4 of -0.59 mmol/L (95 % CI -0.85 to -0.36 mmol/L, p<0.0001) and at week 16: -0.57 mmol/L (95 % CI -0.80 to -0.31 mmol/L, p<0.0001) in the ITT population. Correlations between changes in SFA intake, body weight or physical activity levels and changes in LDL cholesterol concentrations were weak. Therefore, including these variables in the model did not add any information to the analysis. The Panel considers that this study shows an effect of the combination of ingredients in Limicol® on blood LDL-cholesterol concentrations.

The Panel notes that the three human intervention studies, which were conducted by two independent research groups, showed an effect of the combination of 600 mg artichoke leaf dry extract with 30-36 mg caffeoylquinic acids, 500 mg red yeast rice with 2 mg monacolin K, 10 mg sugar-cane derived policosanols, 20 mg French maritime pine bark extract with 18 mg OPC, 30 mg garlic dry extract with 0.25 mg allicin, 30 mg α-tocopherol equivalents, 5 mg riboflavin and 9 mg inositol hexanicotinate in Limicol® on LDL-cholesterol concentrations when consumed daily in three doses with the major meals (Barrat et al., 2012; Barrat et al., 2013; Ogier et al., 2013). The Panel also notes that doubling the dose of the food that is the subject of the health claim did not have an additional effect on LDL-cholesterol concentrations (Barrat et al., 2012).

The applicant claims that monacolins in red yeast rice, sugar cane-derived policosanols and the artichoke leaf extract are the food constituents in Limicol® which are responsible for the claimed effect. The Panel notes the well established role of monacolin K at doses of 10 mg per day in lowering LDL-cholesterol (EFSA NDA Panel, 2011a, 2013). However, the Panel also notes that the available evidence does not establish that any of the other food constituents in Limicol®, including policosanols (EFSA NDA Panel, 2011b) and artichoke leaf extract (Wider et al., 2013), exert an LDL-cholesterol lowering effect in humans on their own, and that at the proposed conditions of use no evidence has been provided for an LDL-cholesterol lowering effect of any of the food constituents in Limicol®, or as to how the ingredients, individually or in any combination, could contribute to the claimed effect.

In weighing the evidence, the Panel took into account that although no evidence was provided for an LDL-cholesterol lowering effect of any of the single food constituents in Limicol® at the proposed conditions of use, or as to how the ingredients, individually or in any combination, could contribute to the claimed effect, and despite the lack of a dose-response relationship observed in one human intervention study, three human intervention studies conducted by two independent research groups showed an effect of the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® on blood LDL-cholesterol concentrations.

The Panel concludes that a cause and effect relationship has been established between the consumption of the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and a reduction in blood LDL-cholesterol concentrations.

The Panel could not have reached its conclusions without the human intervention studies claimed as proprietary by the applicant (Barrat et al., 2012; Barrat et al., 2013; Ogier et al., 2013).

4. Panel's comments on the proposed wording

The Panel considers that the following wording reflects the scientific evidence: "A combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate reduces blood LDL-cholesterol concentrations. High LDL-cholesterol is a risk factor in the development of coronary heart disease."

5. Conditions and restrictions of use

The Panel considers that in order to bear the claim a product should provide 600 mg artichoke leaf dry extract with 30-36 mg caffeoylquinic acids, 500 mg red yeast rice with 2 mg monacolin K, 10 mg sugar-cane derived policosanols, 20 mg French maritime pine bark extract with 18 mg OPC, 30 mg garlic dry extract with 0.25 mg allicin, 30 mg α-tocopherol equivalents, 5 mg riboflavin and 9 mg inositol hexanicotinate in three daily doses to be consumed with the major meals. The target population is adults in the general population wishing to reduce their blood cholesterol concentrations.

In relation to restrictions of use, the Panel refers to the Summary of Product Characteristics of lovastatin-containing medicinal products available on the EU market.

The Panel also refers to the opinion by the EFSA CONTAM Panel on citrinin, a nephrotoxic mycotoxin which can be produced by some strains of *Monascus purpureus* (EFSA CONTAM Panel, 2012).

CONCLUSIONS

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

- The food that is the subject of the health claim, the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol®, is sufficiently characterised.

- The claimed effect proposed by the applicant is "oral consumption of the food supplement Limicol® significantly reduces circulating low-density lipoprotein-cholesterol (LDL-cholesterol) level, thus reducing the risk of coronary heart disease". The target population proposed by the applicant is "males and females from 18 to 65 years with mild to moderate hypercholesterolaemia". Reduction of blood LDL-cholesterol concentrations is a beneficial physiological effect. High LDL-cholesterol is a risk factor in the development of coronary heart disease.

- A cause and effect relationship has been established between the consumption of the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and a reduction in blood LDL-cholesterol concentrations.

- The following wording reflects the scientific evidence: "A combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate reduces blood LDL-cholesterol concentrations. High LDL-cholesterol is a risk factor in the development of coronary heart disease."

- In order to bear the claim a product should provide 600 mg artichoke leaf dry extract with 30-36 mg caffeoylquinic acids, 500 mg red yeast rice with 2 mg monacolin K, 10 mg sugar-cane derived policosanols, 20 mg French maritime pine bark extract with 18 mg OPC, 30 mg garlic dry extract with 0.25 mg allicin, 30 mg α-tocopherol equivalents, 5 mg riboflavin and 9 mg inositol hexanicotinate in three daily doses to be consumed with the major meals. The target population is adults in the general population wishing to reduce their blood cholesterol concentrations.

- In relation to restrictions of use, reference is made to the Summary of Product Characteristics of lovastatin-containing medicinal products available on the EU market and to the opinion by the EFSA CONTAM Panel on citrinin, a nephrotoxic mycotoxin which can be produced by some strains of *Monascus purpureus*.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on Limicol® and reduction of blood LDL-cholesterol concentrations pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0370_FR). January 2013. Submitted by Laboratoire Lescuyer.

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GLOSSARY AND ABBREVIATIONS

ANCOVA	Analysis of covariance
CHD	Coronary heart disease
ITT	Intention-to-treat
LDL	Low-density lipoprotein
OPC	Procyanidolic oligomers
RCT	Randomised controlled trial
SFA	Saturated fatty acid