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V0137 and 'a reduced loss of cognitive function': evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

Abstract

Following an application from Pierre Fabre Medicament, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to V0137, a 'DHA-enriched fish oil', and 'helps to slow the age-related cognitive decline in domains such as memory and executive function'. The food, V0137, which is the subject of the health claim, is sufficiently characterised. The Panel considers that a reduced loss of cognitive function is a beneficial physiological effect. The applicant submitted five human studies for the substantiation of the health claim, four of which were carried out with foods other than V0137. No conclusions could be drawn from these four studies for the scientific substantiation of the claim. The remaining study was a multicentre, randomised, placebo-controlled, 3-years parallel trial in 1,680 subjects of at least 70 years and at risk of cognitive decline. The subjects were distributed to the four following study groups: (i) V0137 + multidomain intervention (MDI; physical and cognitive exercise, nutrition recommendations); (ii) V0137 without MDI; (iii) placebo + MDI; (iv) placebo without MDI. The primary endpoint of the study was a change in cognitive function, as assessed by a composite cognitive score. There were no statistically significant differences between the study groups for changes in the composite cognitive score at 36 months. The Panel concludes that a cause and effect relationship has not been established between the consumption of V0137 and a reduced loss of cognitive function.

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Keywords: V0137, cognition, memory, health claims

Requestor: Competent Authority of France following an application by Pierre Fabre Medicament

Question number: EFSA-Q-2016-00071

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Summary

Following an application from Pierre Fabre Medicament, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to V0137, a 'DHA-enriched fish oil', and 'helps to slow the age-related cognitive decline in domains such as memory and executive function'.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

The approach of the NDA Panel for the evaluation of the health claim is outlined in the European Food Safety Authority (EFSA) general guidance for stakeholders on health claim applications and the specific guidance on health claims related to functions of the nervous system, including psychological functions.

The food that is the subject of the health claim is V0137, which, according to the applicant, is a 'DHA-enriched fish oil'. Detailed information on the composition of the food and its manufacturing process was provided. The Panel considers that the food, V0137, which is the subject of the health claim, is sufficiently characterised.

The claimed effect proposed by the applicant is that consumption of V0137, when accompanied by a multidomain intervention (MDI), helps to slow the age-related decline in domains such as memory and executive function. The target population proposed by the applicant is 'elderly (at least 70 years old) people with primarily spontaneous memory complaints related to mild cognitive decline, and wishing to slow their age-related cognitive decline'. Cognitive function encompasses several domains, including memory, attention (concentration), alertness, learning, intelligence, language and problem solving, which are well defined psychological constructs. The Panel considers that a reduced loss of cognitive function is a beneficial physiological effect.

The applicant submitted five human studies for the substantiation of the health claim. Four of the studies were carried out with foods other than V0137. The Panel considers that no conclusions can be drawn from these four studies for the scientific substantiation of the claim.

One human study was carried out with the food, V0137, which is the subject of the health claim. This study was a multicentre, randomised, placebo-controlled, 3-years parallel trial in 1,680 subjects of at least 70 years and at risk of cognitive decline. The study participants were randomly distributed to one of the four following study groups: (i) V0137 + MDI (physical and intellectual training, together with nutrition recommendations); (ii) V0137 without MDI; (iii) placebo + MDI; (iv) placebo without MDI.

The primary endpoint of the study was a change in cognitive function after 3 years of intervention, as assessed by a composite cognitive score. This composite cognitive score was calculated as the sum of z-scores from various cognitive tests, encompassing episodic memory, orientation to time and place, speed of processing and executive function and verbal fluency. Participants underwent assessments at baseline and at visits after 6, 12, 24 and 36 months.

The main analysis was carried out on a 'modified intention to treat (ITT)' population (n = 1,525). This 'modified ITT' population was defined as all the randomised subjects who were assessed at inclusion/baseline and at least once during follow-up. The differences in changes in the composite cognitive score between the intervention groups were assessed using mixed models for repeated measures. Applying a three-level linear mixed model (with 'continuous' time) with random centre intercept and with random cubic subject slope and intercept, and after correction for multiple comparisons, no statistically significant differences were found between the study groups for changes in the composite cognitive score at 36 months.

The applicant also provided sensitivity analyses on the primary outcome (i.e. composite cognitive score) by considering the per protocol (PP) population (n = 1,435). The PP population excluded non-complying subjects. For the MDI, compliance was defined as an attendance rate of at least 75% of the programme during the first 2 months. For the consumption of the study product, only subjects who did not take any capsule during the study were considered non-compliant and were, thus, excluded. When applying a three-level linear mixed model (with 'continuous' time) with random centre intercept and with random cubic subject slope and intercept, a significant overall difference in the change in composite cognitive score at 36 months was found between the four groups. However, for the (post-hoc) group-wise comparisons no statistically significant differences were found between any groups after correction for multiple comparisons.

The Panel considers that, in this study in 1,680 subjects, consumption over 3 years of V0137, in conjunction with physical and intellectual training, did not have an effect on cognitive function in individuals of at least 70 years with primarily spontaneous memory complaints.

The Panel concludes that a cause and effect relationship has not been established between the consumption of V0137 and a reduced loss of cognitive function.

Table of contents

1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006[1] 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, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) 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).

1.2. Interpretation of the Terms of Reference

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) 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: V0137, a 'DHA-enriched fish oil', and 'helps to slow the age-related cognitive decline in domains such as memory and executive function'.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of V0137, a positive assessment of its safety, nor a decision on whether V0137 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 18(4) of Regulation (EC) No 1924/2006.

2. Data and methodologies

2.1. Data

2.1.1. Information provided by the applicant

Food/constituent as stated by the applicant:

- According to the applicant, the food which is the subject of the health claim is V0137, which is a 'DHA-enriched fish oil'.

Health relationship as claimed by the applicant:

- According to the applicant, the consumption of V0137, when accompanied by a multidomain intervention (MDI; i.e. physical training, intellectual training and nutrition recommendations), helps to slow the age-related decline in domains such as memory and executive function. The applicant hypothesised that the cerebral stimulation through physical and intellectual training may promote the use of the supplemented docosahexaenoic acid (DHA) by the brain cells, which would result in an improved membrane fluidity and synaptic plasticity, thereby maintaining the brain cells' functional capacities while ageing. In turn, increased concentration of DHA in brain may allow training to exert maximal benefits.

Wording of the health claim as proposed by the applicant:

- 'V0137, in association with physical and intellectual training, helps to slow the age-related cognitive decline in domains such as memory and executive function'.

[1] 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.

Specific conditions of use as proposed by the applicant:

- According to the applicant, two capsules of V0137 should be consumed daily, providing 1,500 mg of 'DHA-enriched fish oil'. This supplementation should be accompanied by a MDI comprising physical and intellectual training together with nutrition recommendations.
- The target population proposed by the applicant is 'elderly people with primarily spontaneous memory complaints related to mild cognitive decline, and wishing to slow their age-related cognitive decline'. According to the applicant, mild cognitive decline is an intermediate step in the brain ageing process characterised by cognitive deficits including memory complaints.

2.1.2. Data provided by the applicant

Health claim application on V0137 and 'helps to slow the age-related cognitive decline in domains such as memory and executive function' pursuant to Article 13.5 of Regulation 1924/2006, presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of applications for authorisation of health claims (EFSA NDA Panel, 2011).

As outlined in the EFSA general guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016), it is the responsibility of the applicant to provide the totality of the available evidence.

This health claim application includes a request for the protection of proprietary data (Vellas et al., 2015), in accordance with Article 21 of Regulation (EC) No 1924/2006.

2.2. Methodologies

The general approach of the NDA Panel for the evaluation of health claim applications is outlined in the EFSA general guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016).

The scientific requirements for health claims related to functions of the nervous system, including psychological functions, are outlined in a specific EFSA guidance (EFSA NDA Panel, 2012).

3. Assessment

3.1. Characterisation of the food/constituent

According to the applicant, the food that is the subject of the health claim is V0137, a 'DHA-enriched fish oil'.

The Panel noted that out of the five human studies provided (Chiu et al., 2008; Yurko-Mauro et al., 2010; Sinn et al., 2012; Lee et al., 2013; Vellas et al., 2015), only one study (Vellas et al., 2015) was performed with V0137, while the remaining studies were carried out with DHA from microalgae or fish oils other than V0137. Therefore, the applicant was requested to clarify the food which is the subject of the health claim, and to consider whether the claim refers to V0137 or to DHA from all sources. In reply, the applicant pointed out that the food, which is the subject of the claim, should be V0137, a 'DHA-enriched fish oil', and that the studies carried out with foods other than V0137 were submitted as 'supportive evidence' of the single human study performed with V0137.

Detailed information was provided on the composition of the food, its nutritional value and specifications in relation to its acid value, peroxide value, anisidine value, tocopherol content and microbiological quality.

An overview of the manufacturing process and information on the stability and batch-to-batch analyses were provided.

The Panel considers that the food, V0137, which is the subject of the health claim, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is that consumption of V0137, when accompanied by a MDI (i.e. physical training, intellectual training and nutrition recommendations), helps to slow the age-related decline in domains such as memory and executive function. The target population proposed by the applicant is 'elderly people with primarily spontaneous memory complaints related to mild cognitive decline, and wishing to slow their age-related cognitive decline'. Upon request for clarification, the applicant indicated that 'elderly people' should be understood as defined in the protocol for the study by Vellas et al. (2015), and thus at least 70 years old.

Cognitive function encompasses several domains, including memory, attention (concentration), alertness, learning, intelligence, language and problem solving, which are well defined psychological constructs. An increase, maintenance or reduced loss of cognitive function in one or more of its domains is a beneficial physiological effect (EFSA NDA Panel, 2012).

The scientific evidence for the substantiation of health claims related to one or more specific domains of cognitive function can be obtained from human intervention studies showing an effect on objective measures of the specific domain(s) using standard psychometric tests (e.g. standard 'computerised' or 'paper-and-pencil' tests), established test batteries, or valid and reliable tests for the specific domain(s) that is/are the subject of the claim (EFSA NDA Panel, 2012).

In the study (Vellas et al., 2015) submitted by the applicant, changes in cognitive function were assessed by means of a composite cognitive score. The composite cognitive score was calculated as the sum of z-scores for episodic memory (Free and Cued Selective Reminding Test (FCSRT)) (Grober et al., 1988; Van der Linden et al., 2004), orientation to time and place (10 orientation items on the mini-mental state examination (MMSE) test) (Folstein et al., 1975; Kalafat et al., 2003), speed of processing and executive function (Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale (WAIS)) (Wechsler, 1981, 1989) and verbal fluency (Category Naming Test) (Isaacs and Akhtar, 1972; Cardebat et al., 1990). Given the variety and breadth of these tests, the Panel considers that this composite cognitive score is an adequate outcome measure to assess changes in cognitive function.

The Panel considers that a reduced loss of cognitive function is a beneficial physiological effect.

3.3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed, Science Direct and Google Scholar using search terms such as fish oil, docosahexaenoic acid, DHA, omega-3, cognitive, cognition, brain, adult, old, elderly in order to retrieve controlled and/or randomised clinical trials/studies, observational studies, meta-analyses and systematic reviews in the English or French language. Additional searching was done by hand. Studies were included if they provided at least 250 mg DHA per day and were carried out in healthy adults aged at least 45 years who had subjective or objective memory complaints. Studies were excluded if they were conducted in children or adults younger than 45 years, in subjects of $\geq$ 45 years without subjective or objective memory complaints, or in subjects with a clinical diagnosis of dementia or other psychological or neurological diseases. Studies which did not assess the relationship between the intake of DHA and the claimed effect and studies of a poor methodology were also excluded.

The applicant submitted five human studies (Chiu et al., 2008; Yurko-Mauro et al., 2010; Sinn et al., 2012; Lee et al., 2013; Vellas et al., 2015) for the substantiation of the health claim.

The study by Yurko-Mauro et al. (2010) was performed with DHA from microalgae. The studies by Chiu et al. (2008), Sinn et al. (2012) and Lee et al. (2013), respectively, were carried out with various fish oil preparations other than V0137. The Panel notes that these four studies were performed with foods other than V0137. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

One human study (Vellas et al., 2015, claimed as proprietary by the applicant) was carried out with the food, V0137, which is the subject of the health claim. This study was a multicentre, randomised, placebo-controlled, 3-years parallel trial in 1,680 subjects (male: 35.2%, female: 64.8%) of at least 70 years and at risk of cognitive decline. In order to be eligible, subjects (enrolled at 13 memory clinics) had to have at least one of the three following criteria: (i) a spontaneous memory complaint expressed to their general practitioner, (ii) a limitation in one of the instrumental activities of daily living (IADL), and/or (iii) a slow walking speed ($\leq$ 0.8 m/sec, equivalent to 5 sec to walk 4 m). The vast majority (99%) of the subjects were recruited after subjective memory complaints expressed to the primary care practitioner. Subjects with a diagnosis of dementia or Alzheimer's disease (DSM IV criteria), any other neuropsychological disease, a MMSE score of $<$ 24 or dependence in at least one daily living activity (ADL $<$ 6) were excluded.

The aim of the study was to assess whether the supplementation with V0137 in association with a multidomain intervention, i.e. consisting of physical and intellectual training, together with nutrition recommendations, had an effect on the change in cognitive function in subjects aged 70 years and older. To this end, the study participants were randomly distributed to one of the four following study groups: (i) two capsules of V0137 daily + MDI; (ii) two capsules of V0137 daily without MDI; (iii) placebo (paraffin oil) + MDI; (iv) placebo without MDI. Randomisation was stratified according to site.

The MDI consisted of initial training sessions in small groups (6–8 participants) in twelve 120-min sessions for the first 2 months. Each session included 60 min of cognitive training, 45 min of physical training and 15 min of nutrition advice. Beginning in month 3, 60-min sessions were given each month for the remainder of the study. These sessions included training in the following three areas: cognitive exercise, nutrition and physical activity.

Participants underwent cognitive, functional and biological assessments at baseline and at visits after 6, 12, 24 and 36 months (M6, M12, M24 and M36). The primary endpoint was a change in cognitive function after 3 years of intervention, as assessed by a composite cognitive score. This composite cognitive score was calculated as the sum of z-scores for episodic memory (Free and Cued Selective Reminding Test (FCSRT) (Grober et al., 1988; Van der Linden et al., 2004), orientation to time and place (10 orientation items on the MMSE test (Folstein et al., 1975; Kalafat et al., 2003)), speed of processing and executive function (Digit Symbol Substitution Test from the WAIS (Wechsler, 1981, 1989)) and verbal fluency (Category Naming Test (animals) (Isaacs and Akhtar, 1972; Cardebat et al., 1990)).

A power analysis indicated that 201 participants were required in each group to detect with a power of 80% (and an alpha of 0.0125), a 0.3 SD difference between the four trial arms (three treatment groups + placebo group) in the delayed free recall score of the FCRST after 3 years of intervention. A drop-out rate of 30% was anticipated over the 3 years of intervention and the total sample size was adjusted accordingly. As the study subjects included were in better health than expected by the authors (i.e. percentage of recruited subjects with CDR = 0.5 was around 30–40% instead of the expected 50%), the sample size was increased during the trial. The study authors proposed to change the primary assessment criterion of the study from the free recall score to a composite cognitive score (as described above), which was approved by the Ethics Committee and the Agence Nationale de Sécurité des Médicaments (ANSM) and which, according to the applicant, took place before the unblinding of the study. Following the change in the primary endpoint, the power calculation was revisited, and it was calculated that for a type I risk (alpha) of 0.0125 and 80% power, it would have been necessary to include 248 subjects per group for detecting a difference of 0.3 standard deviations. In order to compensate for an expected dropout rate of 30%, it would have been necessary to include at least 1,420 subjects in the study; this number was reached.

The total dropout rate of the study was 22.9%, and was well balanced between the four study groups (from 22.1% to 23.7%).

According to the statistical analysis plan, the main analysis was to be carried out on a 'modified intention to treat' (ITT) population. The 'modified ITT' population was defined as all the randomised subjects who were assessed (by means of the composite cognitive score) at inclusion/baseline and at least once during follow-up. This 'modified ITT' population amounted to 1,525 subjects (out of 1,680 randomised subjects). The differences in changes in the composite cognitive score between the intervention groups were assessed using mixed models for repeated measures (MMRM; SAS® MIXED procedure). At baseline only, missing scores for any components of the composite score were imputed with the median baseline score. Comparisons were made between the placebo group and each of the three intervention groups (i.e. V0137, V0137 + MDI, placebo + MDI). The alpha significance-level threshold was adjusted by the Hochberg (1988) correction method in order to account for the number of comparisons made. Applying a three-level linear mixed model (with 'continuous' time) with random centre intercept and with random cubic subject slope and intercept, and after correction for multiple comparisons, no statistically significant differences were found between the study groups for changes in the composite cognitive score at 36 months.

The applicant provided sensitivity analyses on the primary outcome (i.e. composite cognitive score) by considering the per protocol (PP) population (n = 1,435). The PP population excluded non-complying subjects. For the MDI, compliance was defined as an attendance rate of at least 75% of the programme during the first 2 months (i.e. at least 9 of the 12 training sessions completed). For the consumption of the study product, only subjects who did not take any capsule during the study were considered non-compliant and were, thus, excluded. Compliance was assessed by comparing the number of soft capsules returned to the number theoretically used by the subject and noted by the investigator in the case report form. Compliance was 71.4% for the MDI and 84% for the consumption of capsules. When applying a three-level linear mixed model (with 'continuous' time) with random centre intercept and with random cubic subject slope and intercept, a significant overall difference ($p = 0.0187$) in the change in composite cognitive score at 36 months was found between the four groups. However, for the (post-hoc) group-wise comparisons, no statistically significant differences were found between any groups after correction for multiple comparisons.

The applicant provided further sensitivity analyses for the 'modified ITT' population, considering separately the effects of the MDI ('yes' vs 'no') and of supplementation with V0137 ('yes' vs 'no') on the composite cognitive score after 36 months. A statistically significant effect was found for the MDI (i.e. the composite cognitive score was improved by 0.080 (standard error = 0.033, CI 0.016–0.145, p = 0.015) in subjects on physical and intellectual training compared to subjects without training), but not for the food (i.e. V0137).

The applicant also provided subgroup analyses for subjects with a Clinical Dementia Rating (CDR) score of 0.5 at enrolment, and for subjects with an MMSE score of no more than 29 (i.e. excluding MMSE scores equal to 30) at enrolment. The Panel considers that in the absence of an effect for the food in the main 'modified ITT' and sensitivity PP analyses, no conclusions can be drawn from these post-hoc exploratory analyses.

The Panel considers that, in this study in 1,680 subjects, consumption over 3 years of V0137, in conjunction with physical and intellectual training, did not have an effect on cognitive function in individuals of at least 70 years with primarily spontaneous memory complaints.

The Panel concludes that a cause and effect relationship has not been established between the consumption of V0137 and a reduced loss of cognitive function.

4. Conclusions

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

- The food, V0137, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is that consumption of V0137 'helps to slow the age-related decline in domains such as memory and executive function'. The target population proposed by the applicant is 'elderly (at least 70 years old) people with primarily spontaneous memory complaints related to mild cognitive decline, and wishing to slow their age-related cognitive decline'. A reduced loss of cognitive function is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of V0137 and a reduced loss of cognitive function.

Steps taken by EFSA

1) Health claim application on V0137, a 'DHA-enriched fish oil', and 'helps to slow the age-related cognitive decline in domains such as memory and executive function' pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0446_FR). Submitted by Pierre Fabre Medicament, 45 place Abel Gance, 92100 Boulogne-Billancourt, France.
2) The application was received by EFSA on 15 January 2016.
3) The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.
4) On 9 February 2016, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
5) On 11 February 2016, EFSA received the missing information as submitted by the applicant.
6) The scientific evaluation procedure started on 15 February 2016.
7) On 21 April 2016, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the scientific evaluation was suspended on 9 May 2016, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
8) On 24 May 2016, EFSA received the applicant's reply and the scientific evaluation was restarted, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
9) During its meeting on 28 June 2016, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to V0137 and a reduced loss of cognitive function.

References

Cardebat D, Doyon B, Puel M, Goulet P and Joanette Y, 1990. Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level. Acta Neurologica Belgica, 90, 207–217.

Chiu CC, Su KP, Cheng TC, Liu HC, Chang CJ, Dewey ME, Stewart R and Huang SY, 2008. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Progress in Neuropsychopharmacology and Biological Psychiatry, 32, 1538–1544.

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011. Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (revision 1). EFSA Journal 2011;9(5):2170, 36 pp. doi:10.2903/j.efsa.2011.2170

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2012. Guidance on the scientific requirements for health claims related to functions of the nervous system, including psychological functions. EFSA Journal 2012;10(7):2816, 13 pp. doi:10.2903/j.efsa.2012.2816

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 38 pp. doi:10.2903/j.efsa.2016.4367

Folstein MF, Folstein SE and McHugh PR, 1975. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189–198.

Grober E, Buschke H, Crystal H, Bang S and Dresner R, 1988. Screening for dementia by memory testing. Neurology, 38, 900–903.

Hochberg Y, 1988. A sharper Bonferroni procedure for multiple tests of significance. Biometrika, 75, 800–802.

Isaacs B and Akhtar AJ, 1972. The set test: a rapid test of mental function in old people. Age and Ageing, 1, 222–226.

Kalafat M, Hugonot-Diener L and Poitrenaud J, 2003. Standardisation et étalonnage français du 'Mini Mental State' (MMS) version GRECO. Revue de Neuropsychologie, 13, 209–236.

Lee LK, Shahar S, Chin AV and Yusoff NAM, 2013. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacology (Berlin), 225, 605–612.

Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J and Howe PR, 2012. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. British Journal of Nutrition, 107, 1682–1693.

Van der Linden M, Coyette F, Poitrenaud J, Kalafat M, Calicis F, Wyns C, Adam S and GREMEM Members, 2004. L'épreuve de rappel libre/Rappel indicé à 16 items (RL/RI-16). In: Van der Linden M, Membres du GREMEM (eds.). *"L'évaluation des troubles de la mémoire"*. Solal, Marseille. 25 p.

Vellas B, Dartigues JF, Touchon J, Dantoine T, Cuffi MN, Bories L, Bordes S, Gasnier Y, Desclaux F, Rouaud O, Bonnefoy M, Robert P, Sudres K and Pesce A, 2015 (unpublished, claimed as proprietary by the applicant). Assessment of the efficacy of omega-3 fatty acids supplementation, multi-domain intervention or their combination on the change of cognitive functions in frail elderly subjects. Study code: 07 116. 3 July 2015.

Wechsler D, 1981. Chapter 4 "Directions for administering the tests". part 7 'Digit symbol'. *Wechsler Adult Intelligence Scale-Revised*. Psychological Corp, New York. 44 p.

Wechsler D, 1989. Chapitre 6 "Consignes pour l'administration et la notation", partie 10 "Codes". In: Centre de Psychologie Appliquée (ECPA) (ed.). *Echelle d'Intelligence de WECHSLER pour adultes (forme révisée)*. Centre de Psychologie Appliquée (ECPA), Paris. pp. 82–83.

Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, Salem N Jr, Stedman M and MIDAS investigators, 2010. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimer's and Dementia, 6, 456–464.

Abbreviations

ADL	activities of daily living
ANSM	Agence Nationale de Sécurité des Médicaments
CDR	Clinical Dementia Rating
DHA	docosahexaenoic acid
FCSRT	Free and Cued Selective Reminding Test
IADL	instrumental activities of daily living
ITT	intention to treat
MDI	multidomain intervention
MMRM	mixed models for repeated measures
MMSE	mini-mental state examination
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
PP	per protocol
WAIS	Wechsler Adult Intelligence Scale