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SCIENTIFIC OPINION

'Citicoline' and support of the memory function: Evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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Abstract

Following an application from Egde Pharma Sp. z o.o, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Poland, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to citicoline and memory. The Panel considers that the food, citicoline (cytidine 5-diphosphocholine, CDP-Choline) inner salt, is sufficiently characterised. Improvement, maintenance or reduced loss of memory is a beneficial physiological effect for middle-aged or elderly adults encountering age-associated subjective memory impairment. The applicant identified three pertinent human intervention studies in healthy individuals that investigated the effect of citicoline on memory. In weighing the evidence, the Panel took into account that only one randomised controlled trial in healthy participants showed a beneficial effect of citicoline on episodic memory when consumed at doses of 500 mg/day for 12 weeks, whereas this effect has not been observed in another study using citicoline at doses of 1 g/day for 3 months or supported by data obtained in patients with dementia using doses of 1 g/day for 12 weeks and 12 months. No convincing evidence of a plausible mechanism by which citicoline or any of its components (in addition to their endogenous synthesis) could exert an effect on memory in humans has been provided. The Panel concludes that a cause-and-effect relationship has not been established between the consumption of citicoline (CDP-Choline) inner salt and improvement, maintenance or reduced loss of memory in middle-aged or elderly adults encountering age-associated subjective memory impairment.

KEYWORDS

CDP-choline, Citicoline, episodic memory, health claim, memory

CONTENTS

1 | INTRODUCTION

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

Regulation (EC) No 1924/2006 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 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: 'Citicoline and support of the memory function'.

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

Information provided by the applicant

See also the section steps taken by EFSA at the end of this opinion.

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is '*Citicoline (cytidine 5-diphosphocholine, CDP-Choline) inner salt*'.

Health relationship as claimed by the applicant

According to the applicant, the health effect is related to '*maintaining efficient memory in the target population of cognitively unimpaired healthy middle-aged and elderly persons encountering subjective memory impairment*.' '*Outcome variables used to assess the claimed effect consisted of a) memory efficacy measures in adult humans correlated with dietary availability of choline; b) evaluation of the effects of oral citicoline, choline, and uridine on the indices of the human memory and on human brain choline compounds; c) evaluation of the effects of oral intake of citicoline and its catabolites on the efficacy of human memory*'.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

The applicant claims that '*the effect of citicoline on some aspects of memory in healthy middle-aged or elderly persons who suffer from age-related memory impairment is likely exerted through combined effects of cytidine and choline, although the effect of choline may prevail*'. '*In humans citicoline following ingestion is well absorbed and rapidly broken down into choline and cytidine. This results in a marked increase of blood choline level, whereas blood cytidine is quickly converted to uridine. Next, choline and uridine enter cells of the human body and join their appropriate metabolic pathways. In an analogy to the term "a prodrug" used in pharmacy to depict a compound which is metabolized in the body to produce an active drug, citicoline shall be called "a pronutrient" that in the human body produces choline and uridine as "active nutrients"*.'

The applicant also claims that 'citicoline activates biosynthesis of phospholipids in neuronal membranes, increases brain metabolism as well as norepinephrine and dopamine levels in the central nervous system, and has neuroprotective effects'.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: 'Citicoline intake supports memory function in healthy middle-aged and elderly persons encountering age-related memory impairment'.

Specific conditions of use as proposed by the applicant

According to the applicant, 'the target population for the intended health claim is healthy middle-aged or elderly adults encountering age-related subjective memory impairment. The quantity of citicoline consumption required to obtain the claimed effect is 500 mg per day'.

Data provided by the applicant

The health claim application on citicoline pursuant to Article 13(5) of Regulation (EC) No 1924/2006 was presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of a health claim application (EFSA NDA Panel, 2021b).

As outlined in the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2021a), it is the responsibility of the applicant to provide the totality of the available evidence.

The applicant has submitted a confidential and a non-confidential version of a dossier following the 'General scientific guidance for stakeholders on health claim applications' (EFSA NDA Panel, 2021a) and the 'Scientific and technical guidance for the preparation and presentation of a health claim application' (EFSA NDA Panel, 2021b).

The application contains data claimed as confidential by the applicant in relation to the Annexes 1, 2, 3 and 4 which include personal data: names, addresses, signatures, email and telephone of natural persons. No confidential data from the application was used in this assessment.

The application does not contain data claimed as proprietary.

In accordance with Art. 38 of Regulation (EC) No 178/2002[1] and taking into account the protection of confidential information and of personal data in accordance with Articles 39 to 39e of the same Regulation, and of the Decision of EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,[2] the non-confidential version of the dossier has been published in the OpenEFSA portal.[3]

2.2 | Methodologies

The approach used by the NDA Panel for the evaluation of health claims is explained in the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2021a). In assessing each specific food/health relationship, which forms the basis of a health claim, the NDA Panel considers the following key criteria:

(i) the food/constituent is defined and characterised;
(ii) the claimed effect is based on the essentiality of a nutrient; OR the claimed effect is defined and is a beneficial physiological effect for the target population and can be measured in vivo in humans;
(iii) a cause-and-effect relationship is established between the consumption of the food/constituent and the claimed effect (for the target group under the proposed conditions of use).

Each of these three criteria needs to be assessed by the NDA Panel with a favourable outcome for a claim to be substantiated. In addition, an unfavourable outcome of the assessment of criterion (i) and/or (ii) precludes the scientific assessment of criterion (iii).

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).

2.3 | Public consultation

According to Art. 32c(2) of Regulation (EC) No 178/2002 and to the Decision of EFSA's Executive Director laying down the practical arrangements on pre-submission phase and public consultations, EFSA carried out a Public Consultation on the non-confidential version of the application from 15 April 2024 to 06 May 2024 (PC-0908) for which no comments were received.

[1]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–48.

[2]Decision https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/210111-PAs-pre-submission-phase-and-public-consultations.pdf.

[3]https://open.efsa.europa.eu/questions/EFSA-Q-2022-00411.

3 | ASSESSMENT

3.1 | Characterisation of the food/constituent

The food/constituent proposed by the applicant as the subject of the health claim is 'citicoline (CDP-Choline) inner salt', hereafter 'citicoline'.

The specifications of citicoline are laid down in the Annex of Commission Implementing Decision authorising the placing on the market of citicoline as a novel food ingredient under Regulation (EC) No 258/97, following a safety evaluation by EFSA (EFSA NDA Panel, 2013).

As described in that Annex, citicoline is a white crystalline powder composed of cytosine, ribose, pyrophosphate and choline with the following chemical names: Choline cytidine 5′-pyrophosphate or Cytidine 5′-(trihydrogen diphosphate), P′-[2-(trimethylammonio) ethyl]ester, hidroxide, inner salt, among other synonyms. The chemical formula is $C_{14}H_{26}N_4O_{11}P_2$. The molecular weight is 488.32 g/mol.

The applicant has provided details on the manufacturing process of the citicoline formulation marketed as Cerebrocholin®. Cerebrocholin® is manufactured biotechnologically with a fermentative process that involves brewer's yeast (*Saccharomyces cerevisiae*). In this process, cytidine monophosphate (CMP) and choline chloride are used as raw materials. Yeast residue is removed by flocculation filter-press to obtain a crude clear solution. Further purification involves chromatography through an anion exchange resin and crystallisation. Information about stability and variability between batches was provided in the application. The Panel notes that the production process of Cerebrocholin® differs from that of 'citicoline (CDP-Choline) inner salt' evaluated by EFSA as novel food ingredient (EFSA NDA Panel, 2013).

Upon EFSA's request, the applicant clarified that the health claim is requested for all citicoline products complying with the specifications laid down in the Annex of the Commission Implementing Decision.

The Panel considers that the food citicoline, 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 'supports memory function'. The proposed target population is 'healthy middle-aged or elderly adults encountering age-related subjective memory impairment', as described by Crook et al. (1987).

Memory is the cognitive ability to maintain previously learned information, so that it may be accessed and used at a later time. Memory is not a unitary construct but instead reflects several distinct cognitive processes (e.g. working memory, explicit memory and implicit memory). Changes in different aspects of memory can be measured using valid psychometric tests (EFSA NDA Panel, 2012).

The Panel considers that the improvement, maintenance or reduced loss of one or more cognitive processes related to memory is a beneficial physiological effect.

3.3 | Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed, Scopus and Web of Science databases using combinations of the following key words: 'citicoline pharmacokinetics and human', 'citicoline and human memory', 'choline and human memory' and 'uridine and human memory'. Only human studies were considered. No other details on the literature search were provided by the applicant. In addition, the applicant provided references with background information on e.g. 'definitions of human memory' and 'healthy aging' compared to 'age-related pathology', among others.

The applicant identified four publications reporting on human intervention studies (Alvarez et al., 1997; Feng et al., 2017; Nakazaki et al., 2021; Spiers et al., 1996) and one narrative review (Winklewski et al., 2018) as being pertinent to the claim. Of these, one human intervention study investigated the effects of citicoline on the neural network connectivity of the corpus callosum in patients with leukoaraiosis by diffusion tension imaging (DTI) (Feng et al., 2017), and the narrative review addressed the state-of-the-art on the use of DTI-derived indices as in vivo surrogate markers of axonal and myelin damage (Winklewski et al., 2018). None of these publications reported on measures of memory. The Panel considers that no conclusions can be drawn from these two publications for the scientific substantiation of the claim.

The applicant also identified one human intervention study (Cotroneo et al., 2013), one systematic review of human intervention studies (Fioravanti & Yanagi, 2005) and two narrative reviews (Alvarez-Sabín & Román, 2011; Fioravanti & Buckley, 2006) on the effects of citicoline in patients suffering from chronic neurological diseases, as supportive evidence. One open-label, non-randomised, parallel trial (Cotroneo et al., 2013) investigated changes in the Mini-Mental State Examination (MMSE, which is a composite cognition score), activities of daily living, magnetic resonance imaging (MRI) of the brain and several physiological parameters. This study did not report on measures of memory and was not considered for the scientific substantiation of the claim. The Panel notes that 11 out of the 14 human intervention studies included in the systematic review are not pertinent to the claim either because of the parenteral administration of citicoline or because memory endpoints were not addressed. Of the remaining studies, one had already been provided by the applicant (Spiers et al., 1996) and two investigated the effect of citicoline administered orally on memory endpoints in patients (Alvarez et al., 1999; Cohen et al., 2003). Both studies will be discussed below (section 'Human intervention studies in patients'). The

Panel considers that no conclusions can be drawn from the systematic review (Fioravanti & Yanagi, 2005) or the narrative reviews (Alvarez-Sabín & Román, 2011; Fioravanti & Buckley, 2006), for the scientific substantiation of the claim.

In the pertinent human studies provided, various tests (e.g. Alzheimer's Disease Assessment scale, Syndrome-Kurztest, Cambridge Brain Sciences Neurocognitive Assessment, Wechsler Memory Scale and Wechsler Memory Scale-Revised, California Verbal Learning Test, Rey Complex Figure Test) have been used to investigate different aspects of the memory construct, such as declarative (explicit) memory (episodic, semantic), short-term memory and/or working memory. In addition, some tests (e.g. Alzheimer's cognitive subscale, Alzheimer's Disease Assessment Scale) have been developed to assess a variety of cognitive functions, including memory, and provide both individual scores for each cognitive function tested and a composite score with the contribution of all functions, including memory. The Panel considers that only scores relative to the memory component are pertinent to the scientific substantiation of the claim.

Human intervention studies in healthy individuals

Three human intervention studies in healthy individuals (Alvarez et al., 1997; Nakazaki et al., 2021; Spiers et al., 1996) have investigated the effect on citicoline on memory (episodic memory, short-term memory and working memory).

In a double-blind, randomised, placebo-controlled, parallel study in the USA (Nakazaki et al., 2021), 100 healthy participants (35 males, 65 females) with age-associated memory impairment (mean age ± SD: 65.5 ± 1.13 and 63.2 ± 1.12 years in the placebo and citicoline groups, respectively) were randomised to either 500 mg/day citicoline (Cognizin® from Kyowa Hakko Bio Co, $n = 49$) or placebo (encapsulated microcrystalline cellulose, $n = 51$) at breakfast for 12 weeks. Citicoline and placebo were identical in colour and size. Compliance was assessed using the number of returned study products and scheduled product intakes at week 6.

Participants were recruited using a database of volunteers and local advertisement based on age (50–85 years) and threshold scores for the MMSE (≥ 24), the Kaufman Brief Intelligence Test – Second Edition (≥ 85), the Geriatric Depression Scale (≤ 5) and the Spatial Span test (3, 4, or 2). Participants with major diseases or taking medications affecting memory and cognition were excluded.

The primary endpoint was change in Spatial Span test scores, a test which assesses visuospatial working memory, between week 0 and week 12. Secondary endpoints for memory were changes in the Monkey Ladder task score (for visuospatial working memory), the Digit Span task score (for short-term verbal memory), the Paired Associate task score (for episodic memory) and a composite memory score from all the above-mentioned memory tests combined. The Panel considers these tests to be valid measures of memory. Other secondary endpoints (tests on selective attention or sustained attention) were not considered as pertinent to the claim. Sample size ($n = 82$) was calculated based on a between-group difference of 9.9% in the Spatial Span score, given a significance level of 5% and a power of 80%. Hundred subjects were recruited to account for possible attrition. A Bonferroni correction was applied for multiple testing leading to an alpha level of 0.00625. Following an intent-to-treat (ITT) approach, a 2-way ANCOVA (including test group, Spatial Span screening score, baseline test scores, sex and BMI) was used to assess differences between the groups for primary and secondary endpoints.

Out of the 100 participants randomised, 99 completed the study. One participant withdrew from the citicoline group due to a headache, possibly related to the study product. Compliance was 99.2% at week 12. No premature unblinding occurred.

A significant effect of citicoline on episodic memory ($p = 0.0025$, Paired Associate task) was observed as compared to placebo, whereas no significant differences between groups were reported for short-term memory (Digital Span task) or working memory (Spatial Span, Monkey Ladder task). The significant effect of citicoline on the composite memory score ($p = 0.0052$) was likely driven by the reported effect on episodic memory.

The Panel considers that this study (Nakazaki et al., 2021) shows an effect of citicoline consumed at a daily dose of 500 mg/day for 12 weeks on episodic memory in healthy subjects aged 50 years and older with age-associated memory impairment, while it does not show an effect on short-term memory or working memory.

In an open-label, randomised controlled trial in Spain with a cross-over design (Alvarez et al., 1997), 24 participants (6 males, 18 females; mean age ± SD: 66.1 ± 10.8 years) with memory deficits (MMSE score: 31.69 ± 2.76) and without dementia were randomised to three arms: (a) 500 mg/day citicoline, (b) 1000 mg/day citicoline or (c) a combination of 300 mg/day citicoline and 90 mg/day nimodipine, for 4 weeks and placebo for another 4 weeks. Half of the participants in each group received active treatment the first 4 weeks and no treatment the next 4 weeks and vice versa for the other half. There was no wash-out period. The Panel notes that no information was provided on the methods used for the recruitment of participants, the compliance to the intervention and the procedure of randomisation used. The Panel also notes that no conclusions can be drawn from the citicoline plus nimodipine arm for the scientific substantiation of the claim.

The Panel notes that the study population included 16 subjects who were receiving drugs for medical conditions, including depression, Parkinson's disease and cerebrovascular disorders, which could affect memory and cognition. The authors reported that eight subjects were medication-free and had only minor memory complaints.

Episodic memory was measured using the Alzheimer's Disease Assessment scale for word recall and word recognition, and the Syndrome-Kurztest for immediate and delayed recall of objects and recognition of objects. The Panel considers these tests as valid measures of episodic memory. No primary endpoint was reported. The Panel notes that the primary outcome of the study was not identified in the publication, that no power calculations were provided, and that multiple comparisons were not considered in the statistical analysis.

Differences in memory test score changes during the study between treatment (all groups combined) and placebo were assessed by analyses of variance (ANOVA) with treatment (yes and no) as the independent factor and testing day (day 1 and day 28) as the repeated measure. The Panel considers that no conclusions can be drawn from this analysis, as the citicoline plus nimodipine arm is not pertinent to the claim. In addition, the non-parametric Wilcoxon test was used to compare paired data before and after treatment, and before and after placebo, for each treatment arm ($n = 8$). The Panel notes that this type of analysis on intra-group changes does not accommodate stratification by sequence group and it does not allow testing for any carry-over effect.

Owing to major methodological limitations (no blinding, no information on compliance or randomization procedure, lack of wash-out period, potential confounding of medications affecting memory, statistical analysis not appropriate for the study design), the Panel considers that no conclusions can be drawn from this study (Alvarez et al., 1997) for the scientific substantiation of the claim.

In a randomised double-blind, placebo-controlled parallel group trial in the USA (Spiers et al., 1996), 95 healthy participants (48 males, 47 females) with age-associated memory impairment were randomised to either 500 mg citicoline twice daily (1 g/day; $n = 48$) or placebo ($n = 47$) for 3 months, after a run-in period of 1 week in which all participants received one tablet of placebo twice daily. Citicoline and placebo were identical in appearance, taste and packaging. Compliance was checked during the study visits at the clinical centre. Only one subject was dropped for noncompliance during the run-in period.

Inclusion criteria were age 50–85 years, MMSE score ≥ 26, a Wechsler Adult Intelligence Scale-Revised score at or above the 25th percentile and having at least average scores for age in the Logical Memory subset of the Wechsler Memory Scale and the Rey-Osterreith Complex Figure tests, which were administered to assess verbal and nonverbal learning. Participants with current or past neurological or psychiatric diseases, or taking medications affecting memory and cognition, were excluded.

Based on a logical memory passage, 49 participants were classified as having relatively inefficient memory if scoring below the mean (stratified by age) for immediate recall (22 in the citicoline and 27 in the placebo group, respectively).

Episodic memory was measured at baseline, at day 30 and day 90 using the Logical Memory subtest stories of the Wechsler Memory Scale and the Wechsler Memory Scale-Revised to test immediate and delayed logical memory. The Panel notes that these tests are valid measures of episodic memory.

Out of the 95 participants randomised, four dropped out for adverse events and one for non-compliance during the run-in, leaving 90 subjects for the Per Protocol (PP) analysis (44 in the citicoline group and 46 in the placebo group).

Repeated measures analysis of covariance (RM-ANCOVA) was used to test the main effect of the treatment and the treatment-by-time interaction. No effect of citicoline on episodic memory (i.e. immediate or delayed logical memory tasks) was observed either in the full sample or in the subsample of participants with relatively inefficient memory.

From the pool of 49 participants with relatively inefficient memory, 32 volunteers (16 initially randomised to citicoline and 16 to placebo) who were willing and able to participate, agreed to switch to the alternative intervention for 2 months after a washout period of 10 days. The Panel notes that the individuals recruited for the unplanned follow-up study were self-selected by their willingness to participate, based on their (relatively inefficient) memory performance and their group assignment in the main study, leading to a loss of randomisation, possible selection bias and loss of blinding. The Panel considers that no conclusions can be drawn from this follow-up study for the scientific substantiation of the claim.

The Panel considers that this study (Spiers et al., 1996) does not show an effect of citicoline consumed at daily doses of 1 g for 3 months on episodic memory in healthy subjects with age-associated memory impairment aged 50 years and older.

Human intervention studies in patients

Two human intervention studies have investigated the effect of citicoline on memory in patients with mild to moderate senile dementia of the Alzheimer type (Alvarez et al., 1999) and in patients diagnosed with vascular dementia (Cohen et al., 2003).

In a randomised, double-blind, placebo-controlled, parallel pilot study conducted in Spain (Alvarez et al., 1999), 30 patients (8 males, 22 females) with mild to moderate senile dementia of the Alzheimer type were randomised in a non-compensatory manner (different number of subjects per group) to either 1 g citicoline/day ($n = 13$) or placebo (tridistilled water, $n = 17$) for 12 weeks.

Inclusion criteria were age ≥ 50 years, probable Alzheimer's disease, a MMSE score between 14 and 26 test and stage 3–6 in the global deterioration scale (GDS). Participants with other diseases, history of any conditions or medications affecting memory and cognition were excluded from recruitment.

The primary endpoints were score changes in the cognitive-function subscale of the Alzheimer's Disease Assessment Scale (ADAS) and in the clinical interview-based impression of change (CIBIC). Secondary endpoints were other scores from the ADAS (total score, memory subtest, noncognitive scale) and MMSE scores (trail making test, performance time and total score). The Panel considers that of the psychometric tests used in this study, only the memory subset of the ADAS is relevant to the claim.

ANOVA was used for between-group analyses of psychometric test scores, with end-of-trial scores as dependent variable and baseline scores as covariate. The statistical analyses were performed on 28 of the 30 randomised patients, presumably the population of completers. No reasons for withdrawal were mentioned in the publication. Subgroup analyses

were also conducted in patients bearing the ε4 allele of the APOE (APOE4, $n = 10$ per treatment group), and in patients with the APOE4 with mild cognitive deterioration (GDS < 5; the number of patients per group is not reported).

No effect of citicoline on the ADAS total score or the ADAS memory subtests was observed. A statistically significant effect of citicoline on the ADAS total score in patients with the APOE4 and the APOE4 plus GDS < 5 is reported in the publication, but not on the ADA memory subtests.

The Panel considers that this pilot study (Alvarez et al., 1999) with methodological limitations does not show an effect of citicoline consumed at daily doses of 1 g for 3 months on episodic memory in patients with mild to moderate senile dementia of the Alzheimer type aged 50 years and older.

In a randomised double-blind, placebo-controlled parallel study conducted in the USA (Cohen et al., 2003), 39 patients with vascular dementia (20 males, 19 females) were randomised to either 500 mg citicoline twice daily (1 g/day) or placebo for 12 months. Placebo and citicoline were identical in appearance, taste and packaging. All patients met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia. The Panel notes that no information is provided in the publication regarding randomisation, allocation concealment, blinding or compliance with the intervention.

Inclusion criteria were age ≥ 55 years and a score between 10 and 24 at MMSE test. Participants with diseases affecting the brain, mental health or cognition, cancers, renal failure or contraindications for brain MRI were excluded.

Participants were given a battery of neuropsychological tests at baseline, at 6 months and at the end of the study (12 months). Of these, the Panel considers the California Verbal Learning Test and the Rey Complex Figure Test to be valid measures of episodic memory and the Digit Span subtest to be a valid measure of short-term memory.

Multivariate analysis of variance (MANOVA) was used to evaluate memory test changes (between baseline, 6 months and 12 months) between groups in completers ($n = 30$). Those who dropped out ($n = 9$) were not different with respect to clinical or demographic characteristics or baseline neurocognitive measures.

No significant differences between the citicoline and placebo groups were reported for measures of either episodic memory or short-term memory.

The Panel considers that this pilot study (Cohen et al., 2003) with methodological limitations does not show an effect of citicoline consumed at daily doses of 1 g for 12 months on episodic memory or short-term memory in patients with vascular dementia 55 years of age and older.

Conclusion on human intervention studies

Three human intervention studies have investigated the effect of citicoline on memory in the target population (i.e. healthy individuals aged 50 years and older with subjective memory impairment). Due to methodological limitations, no conclusions could be drawn from one study (Alvarez et al., 1997). One randomised controlled study (RCT) (Nakazaki et al., 2021) showed that citicoline consumed at doses of 500 mg/day for 12 weeks improved episodic memory as compared to placebo and did not affect short-term or working memory. This beneficial effect of citicoline on episodic memory, however, was not confirmed in a second RCT using higher daily doses of citicoline (1 g) for a similar period (3 months; Spiers et al. (1996)). In addition, the two human intervention studies conducted in patients with dementia of the Alzheimer type (Alvarez et al., 1999) or vascular dementia (Cohen et al., 2003) did not support an effect of citicoline on episodic memory when consumed at doses of 1 g/day for 12 weeks and up to 12 months.

Mechanism of action

The applicant claims that the effect of citicoline on memory could be mediated by the release of choline and cytidine upon consumption, the latter being almost completely converted to uridine in plasma. Both choline and uridine are required in the brain as precursors of neural membrane phospholipids. The applicant also claims that dietary choline is needed to maintain both the integrity of neuronal membranes and acetylcholine synthesis in the brain and that the uptake of circulating choline by the human brain may be impaired with age, which could lead to the impairment of cognitive functions, including memory. According to the applicant, the intake of citicoline under the proposed conditions of use would increase the availability of choline and uridine in the brain, leading to the maintenance of the integrity of neuronal membranes and acetylcholine synthesis and to the improvement of cognitive functions, including memory.

In support of these mechanisms of action, the applicant provided several intervention studies in humans on the effect of choline-containing compounds, including citicoline, on the accrual of different membrane phospholipids in different areas of the brain using magnetic resonance spectroscopy (MRS) techniques, with variable results (Babb et al., 1996, 2002; Cohen et al., 1995; Dechent et al., 1999; Stoll et al., 1995; Tan et al., 1998). Whereas the applicant acknowledges that the available evidence in this area is fragmentary, they argue that one human non-randomised intervention study (Feng et al., 2017) giving 600 mg/day citicoline ($n = 14$) or no citicoline ($n = 16$) for 12 months provided evidence for an effect of citicoline in attenuating the development of leukoaraiosis in the corpus callosum, indirectly assessed by diffusion tensor imaging (DTI). The applicant also argues that two single-arm, uncontrolled human intervention studies, using citicoline supplementation (0.5–2 g/day for up to 6 weeks) showed increased concentrations of brain phosphodiesters and its correlation with improved verbal learning (Babb et al., 2002). Citicoline supplementation was associated with increased concentrations

of brain phosphometabolites related to energy production and utilisation in the anterior cingulate cortex (most affected during healthy ageing) but not the parieto-occipital cortex (Silveri et al., 2008).

The Panel notes the uncontrolled nature of these studies.

The applicant also provided narrative reviews to support that: (a) as choline is a precursor of the neurotransmitter acetylcholine, dietary choline could increase the synthesis of the neurotransmitter acetylcholine, the brain concentrations of which appear to decline with age (Amenta & Tayebati, 2008; McDaniel et al., 2003; Schliebs & Arendt, 2011) and (b) as choline is a precursor of phosphatidylcholine and an important constituent of myelin, and recent studies suggest that the experience-dependent formation of myelin in the circuits encoding memory is an important aspect of how memories are consolidated and recalled (Fields & Bukalo, 2020; Grieb et al., 2021), dietary choline could improve memory through these mechanisms. The Panel notes that these references do not provide convincing evidence that dietary choline improves memory or that endogenous choline synthesis is not sufficient to maintain memory functions.

To support the essential role of dietary choline on cognitive function, including memory, the applicant provided a pilot study with 11 patients (8 males, 3 females) receiving choline-free total parenteral nutrition (TPN) covering >80% nutritional needs for at least 12 weeks prior to study entry (Buchman et al., 2001). Patients were randomly assigned to receive either their usual TPN regime ($n=5$; 37.3 ± 7.3 years; sex not reported) or the TPN plus 2 g/day choline for 24 weeks ($n=6$; 34.0 ± 12.6 years; sex not reported). The Panel notes that no information is provided in the publication regarding randomisation or allocation concealment, and that the intervention was not blinded.

The participants had a battery of neuropsychological tests at baseline and at the end of the study (24 weeks). Among these, the Panel considers that the California Verbal Learning Test and the Rey Complex Figure Test, the Logical Memory subtest stories of the Wechsler Memory Scale (WMS) and Weschler Memory Scale-Revised (WMS-R) Visual Reproduction subtest are valid measures of episodic memory, and that the Digit Span subtest is a valid measure of short-term memory. Wilcoxon rank sum test was used to evaluate memory test changes (between baseline and week 24) between groups. The Panel notes that baseline differences in WMS Logical Memory subtest and WMS-R Visual Reproduction subtest for delayed recall and scores were not considered in the statistical analyses. The Panel also notes that the primary outcome of the study was not identified in the publication and that correction for multiple comparisons ($n=40$ statistical tests performed) was not considered in the statistical analysis.

No significant differences between the choline and placebo groups were reported for measures of memory except for the delayed visual recall subtest of the WMS-R ($p=0.03$), which would not be significant after a correction for multiple testing and considering baseline differences between the choline and placebo groups.

The applicant also provided one prospective cohort study (Framingham Offspring population) on the relationship between choline intake assessed using a food frequency questionnaire and measures of (a) brain atrophy and white matter hyperintensity, and (b) cognitive functions, among which verbal and visual memory, in individuals without dementia (Poly et al., 2011), and one cross-sectional study on the relationship between plasma free choline concentrations and neuropsychological tests of cognitive performance (Nurk et al., 2013). The Panel notes the inherent limitations of these study designs to infer causality, and that memory function was not specifically assessed in the second study.

Finally, the applicant elaborates on the structural role of uridine in brain phosphatide synthesis and its potential effect on synaptic function, acknowledging that no evidence is currently available for an effect of uridine on memory function in healthy older adults.

Overall, the Panel considers that although citicoline, and particularly the choline component, has an established structural role in the synthesis of brain membrane phospholipids and is a precursor of the neurotransmitter acetylcholine, no convincing evidence has been provided for a mechanism by which dietary intake of citicoline or any of its components (in addition to their endogenous synthesis) could beneficially affect memory in older adults with age-associated memory impairment.

Weighing of the evidence

In weighing the evidence, the Panel considers that only one RCT in healthy participants showed a beneficial effect of citicoline on episodic memory when consumed at a dose of 500 mg/day for 12 weeks (Nakazaki et al., 2021), whereas this effect was neither observed in another study using citicoline at a dose of 1 g/day for 3 months (Spiers et al., 1996) nor supported by data from patients with dementia at a dose of 1 g/day for 12 weeks and 12 months (Alvarez et al., 1999; Cohen et al., 2003). The Panel also considers that no convincing evidence has been provided for a mechanism by which the dietary intake of citicoline or any of its components, in addition to their endogenous synthesis, could have a beneficial effect on memory function in older adults with age-associated memory impairment.

The Panel concludes that a cause and effect relationship has not been established between the consumption of citicoline (CDP-Choline) inner salt and improvement, maintenance or reduced loss of memory in middle-aged or elderly adults encountering age-associated subjective memory impairment.

4 | CONCLUSIONS

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

- The food/constituent, citicoline (CDP-Choline) inner salt, is sufficiently characterised.
- The claimed effect proposed by the applicant is 'supports memory function'. The target population proposed by the applicant is 'healthy middle-aged or elderly adults encountering age-related subjective memory impairment'. Improvement, maintenance or reduced loss of memory is a beneficial physiological effect for middle-aged or elderly adults encountering age-associated subjective memory impairment.
- A cause and effect relationship has not been established between the consumption of citicoline (CDP-Choline) inner salt and improvement, maintenance or reduced loss of memory in middle-aged or elderly adults encountering age-associated subjective memory impairment.

DOCUMENTATION AS PROVIDED TO EFSA

Health claim application on pursuant to Article 13.5 of Regulation (EC) No 1924/2006 (Appian number: HC-2022-3292). Submitted by Egde Pharma Sp. z o.o.

STEPS TAKEN BY EFSA

1. This application was received by EFSA on 14/02/2023. The application was validated on 29/04/2024 and the scientific evaluation started.
2. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
3. 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. EFSA sent a first Additional Data Request (ADR1) letter to the Applicant on 06/03/2024. The clock was stopped on 06/03/2024. The clock restarted on 20/03/2024.
4. During its meeting on 07/06/2024, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to "*"Citicoline" and support of the memory function: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006*."

ABBREVIATIONS

ADAS	Alzheimer's Disease Assessment scale
ADR	Additional Data Request
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APOE4	Apolipoprotein E4
BMI	Body mass index
CDP	cytidine diphosphate
CIBIC	clinical interview-based impression of change
CDP-Choline	Cytidine 5-diphosphocholine
CMP	cytidine monophosphate
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DTI	diffusion tension imaging
GDS	global deterioration scale
ITT	Intent to treat
MANOVA	Multiple Analysis of Variance
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NDA	Panel on Nutrition, Novel Foods and Food Allergens
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences
PC	Public consultation
PP	Per protocol
RCT	Randomised controlled trial
RM-ANCOVA	Repeated measures analysis of covariance
SD	Standard deviation
TPN	total parenteral nutrition
USA	United States of America
WMS	Wechsler Memory Scale
WMS-R	Wechsler Memory Scale-Revised

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

Competent Authority of Poland following an application by Egde Pharma Sp. z o.o.

QUESTION NUMBER

EFSA-Q-2022-00411

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