UKNHCC

UK Nutrition & Health Claims Committee

SCIENTIFIC OPINION

Scientific Opinion for the substantiation of a health claim on a combination of lutein, zeaxanthin and *meso*-zeaxanthin and improved visual performance pursuant to Article 13(5) of retained Regulation (EC) No 1924/2006[1], as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020

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Requestor Alliance Pharmaceuticals Ltd

UKNHCC members

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Declarations of interest

The UKNHCC Register of Interests containing all declarations of interests made by members is available at https://www.gov.uk/government/groups/uk-nutrition-and-health-claims-committee#register-of-interests

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Official observers[2]

Alison Black (Welsh Government), Chika Edeh (Food Standards Scotland), Kerry Gribbin (Food Standards Agency Northern Ireland) and Debby Webb (Department of Health and Social Care)

[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.

[2] The UKNHCC Code of Practice states that Official observers attend UKNHCC meetings to provide updates from their respective nations on science and policy matters of relevance whilst respecting UKNHCC independence. For further information on the UKNHCC Code of Practice visit https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/930688/Code_of_Practice_UKNHCC.pdf

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UKNHCC disclaimer

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of a combination of lutein and zeaxanthin and *meso*-zeaxanthin, a positive assessment of its safety, nor a decision on whether a combination of lutein and zeaxanthin and *meso*-zeaxanthin is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of retained Regulation (EC) No 1924/2006[1], as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020.

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 retained Regulation (EC) No 1924/2006[1] as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020.

Claim type

Article 13(5): Function claim based on a (non-essential) beneficial physiological effect

Process undertaken by the UKNHCC

- The application was received by the UKNHCC on 6 April 2021
- The scientific evaluation procedure started on 9 April 2021
- During its meeting on 18 May 2021, the UKNHCC evaluated the evidence submitted by the applicant
- During its meeting on 16 July 2021, the UKNHCC discussed the Scientific Opinion
- Following the meeting, the final Scientific Opinion was agreed via email correspondence

Summary

Following an application from Alliance Pharmaceuticals Ltd submitted for authorisation of a health claim pursuant to Article 13(5) of retained Regulation (EC) No 1924/2006[1] as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020 via the Competent Authority of Great Britain, the United Kingdom Nutrition and Health Claims Committee (UKNHCC) was asked to deliver an opinion on the scientific substantiation of a health claim that "Lutein, zeaxanthin and *meso*-zeaxanthin together improve the visual performance measure known as contrast sensitivity".

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.

The food that is the subject of the health claim is the combination of 10mg lutein, 2mg zeaxanthin and 10mg *meso*-zeaxanthin.

The Committee considers that the food, a combination of lutein, zeaxanthin and *meso*-zeaxanthin, is sufficiently characterised in relation to the proposed claimed effect.

The claimed effect proposed by the applicant is "Lutein, zeaxanthin and *meso*-zeaxanthin together improve the visual performance measure known as contrast sensitivity". The target population is healthy adults.

The Committee considers that improved visual performance is a beneficial physiological effect.

The applicant identified a total of 7 publications, including 5 randomised controlled trials (RCTs) (Loughman et al, 2012; Nolan et al, 2015; Nolan et al, 2016; Stringham et al, 2017a; Stringham et al, 2017b) and 2 reports (Loughman, 2013; Roark & Stringham, 2019) which the applicant suggested met their inclusion criteria to be considered as being pertinent to the claim.

The Committee considers 4 out of 7 publications (Loughman et al, 2012; Roark & Stringham, 2019; Stringham et al, 2017a; Stringham et al, 2017b) as not pertinent to the claim. One report (Loughman et al, 2012) was only available as a conference abstract and another report (Roark & Stringham, 2019) did not assess the effect of the food that is the subject of the claim on visual performance. Two of the RCTs (Stringham et al, 2017a; Stringham et al, 2017b) administered a ratio of lutein, zeaxanthin and *meso*-zeaxanthin which differed from the food that is the subject of the health claim. The Committee considers that no conclusions can be drawn from these publications for the substantiation of the claim.

The Committee considers 3 out of 7 publications (Loughman et al, 2012; Nolan et al, 2015; Nolan et al, 2016) to be pertinent to the claim. Two RCTs (Loughman et al, 2012; Nolan et al, 2015) assessed differences in contrast sensitivity from baseline to 6 months within each group but not between the intervention and placebo groups. Therefore, the Committee considers that no conclusions can be drawn from these 2 RCTs for the substantiation of the claim.

One RCT by Nolan et al (2016) reported an improvement in baseline contrast sensitivity at 6 cycles per degree (cpd) by 0.08 in the group administered 10mg lutein, 2mg zeaxanthin and 10mg *meso*-zeaxanthin (the same ratio proposed by the applicant, in the food that is the subject of the health claim) compared to the placebo group at 12 months. The Committee considers this study to have a risk of bias related to potential selective reporting, in particular due to the main results presented not being analysed according the pre-specified plan published in the protocols (Akuffo et al, 2014; ISRCTN, 2018).

Therefore, in weighing the evidence, the Committee took account of 1 RCT (Nolan et al, 2016) from which conclusions could be drawn.

The Committee concludes there is insufficient evidence to establish a cause and effect relationship between the consumption of 10mg lutein, 2mg zeaxanthin, 10mg *meso*-zeaxanthin together and improved visual performance measured by contrast sensitivity.

Information provided by the applicant

Applicant name and address

Alliance Pharmaceuticals Ltd, Avonbridge House, Bath Road, Chippenham, Wiltshire, SN15 2BB, England.

Food/constituent as stated by the applicant

The food that is the subject of the health claim is a combination of 10mg lutein, 2mg zeaxanthin and 10mg *meso*-zeaxanthin (“LMZ”).

Health relationship as claimed by the applicant

According to the applicant, “Lutein, zeaxanthin and *meso*-zeaxanthin together improves the visual performance measure known as contrast sensitivity (CS)”. Contrast sensitivity refers to the ability of the visual system to discern differences in the luminance of adjacent areas in a face, object, or scene and detect the edges or borders of the target.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: “The combination of lutein, *meso*-zeaxanthin and zeaxanthin helps maintain normal visual performance by maintaining clarity and contrast of sight.”

Specific conditions of use as proposed by the applicant

The applicant has proposed a daily intake of 10mg lutein, 10mg *meso*-zeaxanthin and 2mg zeaxanthin (22mg total carotenoids) for a minimum of 12 months to show a beneficial effect in contrast sensitivity. The proposed target population is healthy adults.

Documentation provided

Health claim application on lutein, zeaxanthin and *meso*-zeaxanthin together improve the visual performance measure known as contrast sensitivity pursuant to Article 13(5) of retained Regulation (EC) No 1924/2006[1], as amended by the Nutrition (Amendment etc.) (EU Exit) Regulations 2019 and the Nutrition (Amendment etc.) (EU Exit) Regulations 2020. Application ID: 001UKNHCC. Submitted by Alliance Pharmaceuticals Ltd.

Assessment

1. Characterisation of the food/constituent

1.1. The food that is the subject of the health claim is a combination of 10mg lutein, 2mg zeaxanthin and 10mg *meso*-zeaxanthin derived from the marigold plant (*Tagetes erecta).* The food also contains sunflower seed oil (75% to 85%) and other ingredients including alpha-tocopherol (0.1% to 1%).

1.2. Lutein, zeaxanthin, and *meso*-zeaxanthin are xanthophyll carotenoids naturally present in foods. These xanthophylls can be measured in foods by established methods. The Chemical Abstracts Service numbers: lutein (127-40-2), zeaxanthin (144-68-3), and *meso*-zeaxanthin (31272-50-1).

1.3. The applicant provided an overview of the manufacturing process with reference to accreditations; GMP, FSSC 22000, HACCP, ISO 9001:2015. A certificate of analysis was provided. No batch-to-batch analysis or information of analytical methods for carotenoids were provided.

1.4. The Committee considers that the food, a combination of 10mg lutein, 2mg zeaxanthin and 10mg *meso*-zeaxanthin, which is the subject of the health claim, is sufficiently characterised in relation to the claimed effect.

2. Relevance of the claimed effect to human health

2.1. The claimed effect proposed by the applicant is “Lutein, zeaxanthin and *meso*-zeaxanthin together improve the visual performance measure known as contrast sensitivity (CS)”. The target population proposed by the applicant is healthy adults.

2.2. The applicant proposed that the fixed combination of 10mg lutein, 10mg *meso*-zeaxanthin and 2mg zeaxanthin should be consumed once daily for a minimum of 12 months in order to achieve the claimed effect.

2.3. Vision is a defined function of the eye and nervous system. An increase in vision, reduced loss of vision or maintenance of vision is a beneficial physiological effect

for the general population. Visual performance can be measured by using standard tests of visual acuity and contrast sensitivity (EFSA, 2012).

2.4. Changes in contrast sensitivity have been proposed by the applicant as the outcome measure of improved visual performance.

2.5. Contrast sensitivity refers to the ability of the visual system to discern differences in the luminance of adjacent areas in a face, object, or scene, and detect the edges or borders of the target.

2.6. The Committee considers contrast sensitivity to be a suitable outcome measure for the scientific substantiation of claims related to increased vision, reduced loss of vision and maintenance of vision.

2.7. The Committee considers that an improvement in visual performance is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

3.1. The Committee notes that a claim on lutein in combination with zeaxanthin and improved vision under bright light conditions has been assessed by the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) with an unfavourable outcome (EFSA, 2014). A further claim on *meso*-zeaxanthin and maintenance of normal vision has been assessed by the EFSA NDA Panel, also with an unfavourable outcome (EFSA, 2010).

3.2. The applicant performed literature searches in Proquest (searching in Embase and Medline) and PubMed using the search terms: (lutein AND zeaxanthin AND meso) AND "contrast sensitivity". The original search was carried out on 21 September 2020 and was repeated on 11 March 2021. Inclusion and exclusion criteria applied to select the pertinent publications were reported. The applicant included publications on healthy human subjects and all study designs. The applicant excluded single ingredient studies, studies with contrast sensitivity as a secondary endpoint and studies which did not include contrast sensitivity as an endpoint.

3.3. The applicant identified a total of 7 publications, including 5 randomised controlled trials (RCTs) (Loughman et al, 2012; Nolan et al, 2015; Nolan et al, 2016; Stringham et al, 2017a; Stringham et al, 2017b) and 2 reports (Loughman, 2013; Roark & Stringham, 2019).

3.4. The Committee considers 4 out of 7 publications (Loughman et al, 2012; Roark & Stringham, 2019; Stringham et al, 2017a; Stringham et al, 2017b) as not pertinent to the claim.

3.5. The applicant noted that there was no full text available for Loughman (2013) and the Committee considers that, as this report was only available as a conference abstract, it could not be evaluated. A report by Roark & Stringham (2019) provided a description of visual acuity, the measurement of contrast sensitivity and the role of macular carotenoids in visual performance including a summary of the Nolan et al (2016) trial. However, the Committee considers that no conclusions can be drawn from this report, as it did not evaluate evidence for the effects of the food that is the subject of the claim on visual performance.

3.6. Two double-blind, randomised, placebo-controlled trials (Stringham et al, 2017a; Stringham et al, 2017b) investigated the effects of lutein, zeaxanthin and *meso*-zeaxanthin together on contrast sensitivity at a different ratio compared to the applicant's food that is the subject of the health claim. Stringham et al (2017a) used 2 carotenoid ratios of 10.86mg lutein, 1.33mg zeaxanthin and 0.94mg *meso*-zeaxanthin in a 12mg supplement and 22.33mg lutein, 2.70mg zeaxanthin and 2mg *meso*-zeaxanthin in a 24mg supplement. Stringham et al (2017b) used a carotenoid ratio of 83% lutein, 10% zeaxanthin and 7% *meso*-zeaxanthin in a 24mg supplement. Therefore, the Committee considers that no conclusions can be drawn from these 2 RCTs for the substantiation of the claim.

3.7. The Committee considers 3 out of 7 publications (Loughman et al, 2012; Nolan et al, 2015; Nolan et al, 2016) as pertinent to the claim.

3.8. A randomised, single-blind, placebo-controlled trial (Loughman et al, 2012) was carried out in 36 healthy adults and was previously evaluated by the EFSA NDA Panel in relation to a claim on lutein and zeaxanthin on improved vision under bright light conditions (EFSA, 2014). Participants were randomised to receive 20mg lutein and 2mg zeaxanthin (n=12); 10mg lutein, 2mg zeaxanthin, and 10mg *meso*-zeaxanthin (n=12); or placebo (n=12) for 6 months. Contrast sensitivity was measured using the Optec6500 Vision Tester with sine wave gratings presented as Gabor patches at spatial frequencies of 1.5, 3, 6, 12, and 18 cycles per degree (cpd). The results for each group by time repeated measures ANOVA were provided. There was no test for a difference in contrast sensitivity at 6 cpd between the intervention group supplemented with 10mg lutein, 2mg zeaxanthin, and 10mg *meso*-zeaxanthin compared to the placebo group, only within group differences in contrast sensitivity from baseline to 6 months were assessed. The Committee considers that the study duration of 6 months is relevant to the scientific assessment, noting that the applicants' conditions of use for the claim is 12 months. The Committee considers that no conclusions can be drawn as differences in contrast sensitivity between the intervention and placebo groups from baseline to 6 months were not assessed.

3.9. A randomised, double-blind, placebo-controlled trial (Nolan et al, 2015) was carried out in 62 adults and including 31 patients with Alzheimer's disease. The Committee considers that the Alzheimer's disease study arm was not the relevant target population for the claimed effect. The healthy participants (n=31)

were randomised to receive 10mg *meso*-zeaxanthin, 10mg lutein and 2mg zeaxanthin (n=15) or placebo (sunflower oil) (n=16) for 6 months. Contrast sensitivity was measured using the Thomson Test Chart Pro 2000[3] using Sloan letterset as the test stimuli at 1.2, 2.4, 6, 9.6 and 15.15 cpd. There was no test for a difference in contrast sensitivity between the intervention group compared to the placebo group, only within group differences in contrast sensitivity from baseline to 6 months were assessed. The Committee considers that the study duration of 6 months is relevant to the scientific assessment, noting that the applicants' conditions of use for the claim is 12 months. The Committee considers that no conclusions can be drawn as differences in contrast sensitivity between the intervention and placebo groups from baseline to 6 months were not assessed.

3.10. In a double-blind, randomised, placebo-controlled trial, Central Retinal Enrichment Supplementation Trials (CREST) by Nolan et al (2016), 53 participants received 10mg lutein, 2mg zeaxanthin and 10mg *meso*-zeaxanthin (the same ratio proposed by the applicant in the food that is the subject of the health claim) in sunflower oil and 52 participants were given a placebo (sunflower oil) for 12 months. The primary outcome was contrast sensitivity at 6 cpd, measured using the Thomson Test Chart Pro 2000[3] and the Sloan letterset as the test stimuli. There were 42 participants in the intervention group and 36 in the placebo group included in the final analysis after dropouts and further exclusion due to macular pigment optical density measurements being greater than 0.55 optical density. Results from the repeated measures analysis showed a significant time by group interaction, with contrast sensitivity at 6 cpd being higher by 0.08 in the intervention group compared with the placebo group at 12 months (p=0.002). Contrast sensitivity was also higher for 1.2 cpd compared with placebo but not at 2.4, 9.6 or 15.5 cpd. The Committee considers this study to have a risk of bias related to potential selective reporting, in particular due to the main results presented not being analysed according to the pre-specified plan published in the protocols (Akuffo et al, 2014; ISRCTN, 2018).

4. Weighing the evidence

4.1. In weighing the evidence, the Committee took account of 1 RCT (Nolan et al, 2016) from which conclusions could be drawn.

4.2. The Committee concludes there is insufficient evidence to establish a cause and effect relationship between the consumption of 10mg lutein, 2mg zeaxanthin, 10mg *meso*-zeaxanthin together and improved visual performance measured by contrast sensitivity.

[3] Test Chart 2000 Xpert; Thomson Software Solutions, Hatfield, UK

Conclusions

On the basis of the data presented by the applicant, the Committee concludes that:

- The food, a combination of 10mg lutein, 2mg zeaxanthin and 10mg *meso*-zeaxanthin, which is the subject of the health claim, is sufficiently characterised in relation to the claimed effect
- The claimed effect relates to improved visual performance. The target population is healthy adults. Improved visual performance is a beneficial physiological effect
- A cause and effect relationship has not been established between the consumption of a combination of 10mg lutein, 2mg zeaxanthin and 10mg *meso*-zeaxanthin and improved visual performance due to insufficient evidence

References

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Abbreviations

ANOVA	Analysis of Variance
CPD	Cycles per degree
CREST	Central Retinal Enrichment Supplementation Trials
CS	Contrast sensitivity
EC	European Commission
EFSA	European Food Safety Authority
FSSC	Food Safety System Certification
GMP	Good manufacturing practice
HACCP	Hazard Analysis and Critical Control Point
ISO	International Organisation for Standardisation
NDA	Panel on Dietetic Products, Nutrition and Allergies
RCT	Randomised Controlled Trial
UKNHCC	United Kingdom Nutrition and Health Claims Committee