

## Commissioning Statement

<b>Treatment</b>	<b>Antioxidant vitamins</b>
<b>For the treatment of</b>	Slowing the progression of advanced age-related macular degeneration (AMD)
<b>Commissioning position</b>	<p><b>NHS Calderdale CCG does not routinely commission the use of antioxidant vitamin preparations to treat AMD.</b></p> <p><b>Patients may opt to purchase these preparations over-the-counter.</b></p> <p><b>Do not start new patients.</b></p>
<b>Date effective from</b>	11.09.2017
<b>Policy to be reviewed by</b>	10.09.2020 <i>(to be reviewed before this once NICE issues their clinical guideline on AMD)</i>
<b>Background information</b>	<p>AMD is a condition affecting the central area of the retina. The retina can deteriorate with age and some people develop lesions that can lead to loss of central vision [1]. It has been suggested that progression of the disease may be slowed down in people who eat a diet rich in antioxidant vitamins.</p> <p>A number of antioxidant vitamin-based nutritional supplements are marketed with promotional claims that they improve eye health. These preparations are unlicensed as medicinal products.</p> <p>NICE has not issued guidance on antioxidant vitamins for AMD, but a clinical guideline on macular degeneration is due to be published in January 2018. The final scope includes strategies for reducing the risk of developing AMD in the unaffected eye or progressing to late AMD, including smoking cessation, increasing the intake of antioxidants, carotenoids and omega 3 fatty acids through dietary changes or high-dose vitamin and mineral supplementation [2].</p>
<b>Summary of evidence/rationale</b>	<p>The rationale for not routinely commissioning antioxidant vitamins for AMD is as follows:</p> <ul style="list-style-type: none"> <li>• The marketed nutritional supplements are not licensed as medicinal products;</li> <li>• The Royal College of Ophthalmologists AMD guidelines say that it is difficult to generalise the results from the AREDS studies, which studied relatively well-nourished American people, to other populations. Antioxidant supplements are generally safe, but harmful effects are possible [3].</li> </ul>

	<p><b>Effectiveness</b></p> <p><u>Age-Related Eye Disease Study Research Group</u>          This study (n=3,640) assessed the effect of high doses of zinc and/or antioxidant vitamins on the development and progression of AMD [4]. 67% of participants also took Centrum®, a multivitamin preparation. The pre-defined plan was to pool results from participants in categories 2, 3 and 4 but there were too few people in category 2. Researchers needed a sample size of at least 3,600 people to detect an effect on progression to advanced AMD. Subgroup analysis (based on 2,556 participants in categories 3 and 4) suggested that only patients with advanced disease benefited from zinc plus antioxidants. However, this should be treated with caution due to the analysis being underpowered.</p> <p>No effect was seen on visual acuity for groups 2 – 4. A statistically significant result was achieved when sub-group analysis was undertaken for categories 3 and 4 for antioxidant plus zinc.</p> <p>Participants from the AREDS study were followed up for 5 years in an epidemiological study [5]. The beneficial effects from the supplement persisted for development of neovascular AMD but no effect was seen on central geographic atrophy. Patients who took antioxidant vitamins were more likely than those who did not to report yellowing of the skin or to require hospital admission for infection.</p> <p><u>Age-Related Eye Disease Study 2 Research Group</u>          This follow up study (4,203 predominantly well-nourished, white participants) to AREDS assessed the effect of the original formulation (vitamins C and E, beta-carotene and zinc) plus lutein, zeaxanthin and omega-3 fatty acids on the risk of progression to AMD [6]. The addition of lutein and zeaxanthin, omega-3 fatty acids, or both, to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD. The authors concluded that there was insufficient evidence to recommend the use of zinc.</p> <p>However, participants who took supplementary lutein and zeaxanthin who normally had a low dietary intake of lutein and zeaxanthin demonstrated a small protective effect for progression to advanced AMD (but based on sub-group analysis).</p> <p>A dose-response relationship remains to be evaluated, as only one dose of supplement was used in the trial [7].</p> <p><u>The Carotenoids in Age-related Maculopathy trial</u>          This trial looked at patients with early AMD in both eyes or late choroidal neovascularisation or geographic atrophy in 1 eye in patients randomised to antioxidant (n=216) or placebo (n=217) [8]. The antioxidant delivered 12mg lutein, 0.6mg zeaxanthin,</p>
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	<p>15mg vitamin E, 150mg vitamin C, 20mg zinc oxide and 0.4mg copper gluconate. No difference in the primary outcome of best-corrected visual acuity was found between the groups at 12 months.</p> <p><u>The Cochrane Collaboration</u> - Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration</p> <p>The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of AMD in people with AMD [9]. Thirteen trials (6,150 participants) were included in this review. Over half the participants (3,640) were randomised in one trial (AREDS in the USA), which found a beneficial effect of antioxidant (beta-carotene, vitamin C and vitamin E) and zinc supplementation on progression to advanced AMD (adjusted odds ratio (OR) 0.68, 95% confidence interval (CI) 0.53 to 0.87) over an average of 6.3 years. Overall the authors considered the strength of the evidence to be moderate.</p> <p>The authors concluded that people with AMD may experience delay in progression of the disease with antioxidant vitamin and mineral supplementation. This finding is drawn from one large trial conducted in a relatively well-nourished American population. The generalisability of these findings to other populations is not known.</p> <p>A further Cochrane Review found accumulating evidence that vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD [10]. There is no evidence for other antioxidant supplements.</p> <p><b>Safety</b>          Although generally regarded as safe, vitamin supplements may have harmful effects. For example, zinc supplementation is associated with a small increase in the risk of hospitalisation due to prostatic hyperplasia and urinary tract infections [4]. For people with vascular disease or diabetes mellitus there is a possibility of a small increased risk of heart failure associated with vitamin E supplementation [11]. Beta-carotene has been found to increase the risk of lung cancer in smokers [4].</p> <p>The Cochrane Review suggests that a systematic review of the evidence on harms of vitamin supplements is needed [9].</p> <p><b>Advice for patients</b>          The Beaver Dam eye study showed that smoking is linked to a 2-fold increase in the risk of AMD [12]. The Royal College of Ophthalmologists' guidelines on management of AMD recommend that patients should be given advice on smoking cessation [3].</p>
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	<p>Encourage patients to eat a healthy diet rich in vegetables, fruit, oily fish and eggs [3].</p> <p>Patients should be advised to have regular eye examinations [3].</p> <p>References</p> <ol style="list-style-type: none"> <li>1. NHS Choices. Macular degeneration – symptoms. 24.8.2015. Accessed from <a href="http://www.nhs.uk/Conditions/Macular-degeneration/Pages/Symptoms.aspx">http://www.nhs.uk/Conditions/Macular-degeneration/Pages/Symptoms.aspx</a> on 28.6.2017</li> <li>2. NICE. Clinical Guideline in development (GID-CGWAVE0658). Macular degeneration. Accessed from <a href="https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0658">https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0658</a> on 9.5.2017</li> <li>3. Royal College of Ophthalmologists. Age-related macular degeneration: Guidelines for management 2013. Accessed from <a href="https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf">https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf</a> on 9.5.2017</li> <li>4. Age-Related Eye Disease Study Research Group. A randomised, placebo-controlled, clinical trial of high-dose supplementation with Vitamins C and E, beta-carotene, and zinc for age-related macular degeneration and vision loss. Archives of Ophthalmology 2001;119: 1417-36</li> <li>5. Chew EY, Clemon TE, Agron E et al. Long-Term Effects of Vitamins C, E, Beta-Carotene and Zinc on Age-Related Macular Degeneration. AREDS Report No. 35. Ophthalmology 2013;120(8):1604-11</li> <li>6. AREDS2 Research Group. Lutein/Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration. The Age-Related Eye Disease Study 2 (AREDS2) Controlled Randomized Clinical Trial. JAMA 2013; 309(19):2005-15</li> <li>7. Musch DC. Editorial. Evidence for Including Lutein and Zeaxanthin in Oral Supplements for Age-Related Macular Degeneration. JAMA Ophthalmology 2014;132(2):139-41</li> <li>8. Beatty SS. Visual Outcome After Antioxidant Supplementation. Ophthalmology 2013;120(3):645</li> <li>9. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2012, Issue 11. Art.No.: CD000254. DOI: 10.1002/14651858.CD000254.pub3.</li> <li>10. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD000253. DOI: 10.1002/14651858.CD000253.pub3</li> <li>11. NICE Clinical Knowledge Summaries. Macular degeneration – age-related. Last updated March 2016. Accessed from <a href="https://cks.nice.org.uk/macular-degeneration-age-related#!topicsummary">https://cks.nice.org.uk/macular-degeneration-age-related#!topicsummary</a> on 9.5.2017</li> <li>12. The Beaver Dam Eye Study. Accessed from <a href="http://www.bdeyestudy.org/">http://www.bdeyestudy.org/</a> on 18.5.2017</li> </ol>
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