Antioxidant supplements for the prevention of age-related macular degeneration

This is one of a number of bulletins providing further information on medicines that should be given a low priority, are poor value for money, suitable for self-care or for which there are safer more suitable alternatives. This guidance will support Clinical Commissioning Groups (CCGs) in taking action on items that should not routinely be prescribed in primary care or on the NHS.

Further bulletins, including the overarching low value medicines information bulletin are available on the PrescQIPP website, available at https://www.prescqipp.info/drop-list/headline-areas/the-prescqipp-drop-list#low-value-medicines-lvm

This bulletin focuses on antioxidant supplements for the prevention of age-related macular degeneration (AMD). Within the context of this bulletin, the term ‘antioxidant supplement’ is generally used in reference to products marketed for eye health. The bulletin provides the rationale for discontinuing supply of such products on NHS FP10 prescriptions as there is a lack of robust evidence of clinical effectiveness.

Recommendations

- As the balance of benefits and risks of taking antioxidant supplements for AMD is not currently clear, they are not recommended for prescribing.
- Discontinue prescribing antioxidant vitamins for the prevention of AMD on FP10 and do not initiate new prescriptions. An appropriate policy on the prescribing of these supplements, discussed with local specialists, should be in place before such work is undertaken.
- Inform patients and provide them with information about the change.
- Self-management support and advice for AMD should include a discussion about smoking cessation (where relevant), diet, and sources of practical and emotional support.¹
- People who wish to purchase antioxidants marketed for eye health should discuss them with their GP before taking them.
- People who smoke, former-smokers, and those who have been exposed to asbestos should not take supplements containing beta-carotene. Beta-carotene supplementation has been associated with an increased risk of lung cancer in some groups.²⁻⁴

Background

In England and Wales, over £1.6 million is spent annually on antioxidant supplements for eye health (ePACT July 2017 - September 2017). Discontinuing the prescribing of these products has the potential to release significant savings. It is hoped that GPs will review patients accordingly and realise the cost savings.
Age-related macular degeneration (AMD)

Age-related macular degeneration is the term applied to changes, without any other obvious precipitating cause, which occur in the central area of the retina (macula) in people aged 55 years and above. It is the commonest cause of severe visual impairment in older adults in the developed world. The early stages of AMD are generally asymptomatic. They are characterised by atrophy of cells in the retina, build-up of drusen (deposits of lipid and protein under the retina) and pigmentary changes in the macula. Late AMD takes two forms, both of which cause loss to central vision:

- Late ‘dry’ AMD where atrophy affects the centre of the macula, which progresses slowly.
- Late ‘wet’ (or neovascular) AMD where abnormal blood vessels grow into the macula and leak blood or fluid. This type of AMD can advance very quickly.

Although intraocular drugs that inhibit vascular endothelial growth factor are available for treating late ‘wet’ active AMD, no effective therapies are proven for late ‘dry’ AMD.

Antioxidant supplements

It is thought that the retina may be particularly vulnerable to oxidative stress from free-radicals because of its exposure to visible light and high oxygen concentrations. There has been considerable interest in antioxidant micronutrients and their possible protective role against AMD development and progression. Much of this interest has focused on carotenoids (in particular beta-carotene, lutein and zeaxanthin), vitamin C, vitamin E and zinc, which are all common in the diet and have antioxidant properties.

The antioxidant formulations that have undergone the most study are the AREDS and AREDS2 formulas, named after the studies investigating them (see ‘Clinical effectiveness’).

The AREDS formula consists of:

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Beta-carotene</td>
<td>15mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400IU</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>500mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>80mg</td>
</tr>
<tr>
<td>Copper</td>
<td>2mg (to prevent copper deficiency that can result from high dose zinc supplementation, and can lead to anaemia)</td>
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The AREDS2 study tested several supplement combinations. However, ‘AREDS2 formula’ usually refers to the same vitamin C, vitamin E and copper doses as in AREDS. Beta-carotene is replaced with lutein (10mg) and zeaxanthin (2mg), which are the main components of the macular pigment. A lower dose of zinc (25mg) may be included.

A number of antioxidant supplements marketed for eye health are available to purchase. They are classed as food supplements, and are not licensed as medicines. One antioxidant supplement, MacuLEH Light®, has been classified as a borderline substance by the Advisory Committee on Borderline Substances (ACBS). It can be prescribed on an NHS prescription (endorsed ‘ACBS’) for use ‘following assessment by a Consultant Ophthalmologist for patients with a specific stage of AMD’. MacuLEH Light® contains an AREDS2 type formula. The evidence review and conclusions of the National Institute of Health and Care Excellence (NICE), discussed below, should therefore apply equally to this product as they do to similar products that have not been designated ‘ACBS’ status.
National guidance

In May 2017, NICE published draft clinical guidance on the diagnosis and management of AMD. The final version of the guideline is expected to be published in January 2018.

In the NICE draft guideline, no treatment recommendation is made in relation to antioxidant supplements in AMD. Although their review of the evidence suggested a positive effect of antioxidant supplements on slowing progression to late AMD, the Guideline Committee had reservations about the studies that made them sceptical about the treatment effects (see ‘Clinical effectiveness’). They were also unable to conclude whether the treatment benefits of the antioxidant supplements studies outweigh the potential risks that could be caused by individual components of the antioxidant supplements (see ‘Adverse effects’).

The committee agreed to make a research recommendation to investigate the effectiveness and cost-effectiveness of antioxidant supplements on AMD disease progression for those at high risk. They felt that a large randomised controlled trial (RCT) comparing the AREDS2 formula with no treatment (i.e. normal diet) was needed.

At the time of publication of this bulletin only the draft version of the NICE clinical guideline for AMD was available. Draft NICE guidance is subject to stakeholder consultation and the final version of the guidance may differ.

A 2013 guideline from the Royal College of Ophthalmologists states that AREDS-type supplements may be indicated in people with intermediate AMD or advanced AMD in one eye.

A Clinical Knowledge Summary on AMD states that, when a person has been advised to take this type of antioxidant supplement, the AREDS2 formula is generally recommended. It states that previously recommended supplements containing beta-carotene are not now recommended.

Clinical effectiveness

Prevention or slowing of progression of established AMD

A Cochrane review assessed the effects of antioxidant supplements on the progression of AMD in people with AMD. Nineteen trials were included. Most of the evidence supporting antioxidant supplements for slowing the progression of AMD came from one large study (n=3640), the Age-Related Eye Disease Study (AREDS, see below). The study was conducted in a relatively well-nourished American population and the generalisability of its findings to other populations is not known. The authors note that supplements containing lutein and zeaxanthin are heavily marketed for people with AMD, but that their review shows they may have little or no effect on the progression of AMD.

For NICE’s review of antioxidant supplements in slowing the progression of AMD, fourteen studies met the inclusion criteria. By far the largest of these were the AREDS and the AREDS2 studies.

The AREDS study was a double-blind, placebo-controlled RCT that investigated the use of a high-dose antioxidant vitamins and zinc supplement in people with AMD. It enrolled people with borderline, mild or intermediate AMD features in one or both eyes, plus people with advanced AMD or vision loss due to AMD in one eye only. The primary outcomes were based on progression to advanced AMD and reduction in visual acuity. Average follow up was 6.3 years. Overall, there was a statistically significant odds reduction for the progression to advanced AMD in the antioxidants plus zinc group compared with placebo; odds ratio 0.72 (99% confidence interval 0.52 to 0.98).

Very few people with mild or borderline AMD at baseline actually progressed to advanced AMD. The investigators felt that this made it impossible to assess treatment effects on AMD for this category, and less likely that treatment would be recommended. They therefore undertook an analysis that excluded those with early or borderline AMD at baseline, which gave an odds ratio of 0.66 (99% confidence interval 0.47-0.91) and a relative risk reduction of 25%. It was only in this higher-risk group...
that a statistically significant reduction in rates of visual acuity loss was observed with the antioxidant supplement. The investigators acknowledge that the treatment benefit seen in AREDS is modest and that participants in all treatment arms continued to progress to advanced AMD and lose vision over time.\(^7\)

The NICE Guideline Committee expressed reservations about AREDS analyses based on a higher-risk subgroup, due to the risk of selection bias affecting the results. They questioned the generalisability of the findings, as 20% of participants had been taking multivitamins containing a supplement supplied via the study protocol prior to enrolment in the study (meaning that participants were unlikely to be representative of the general population). Furthermore, the treatment effects reported in AREDS were not confirmed by the other AMD prevention trials included in NICE’s analysis. Safety concerns were also noted.\(^1\)

A second large study, AREDS2 (n=4230), was designed to test whether adding carotenoids lutein and zeaxanthin or omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid), or both, to the original AREDS formulation might further reduce the risk of progression to advanced AMD. There was no true placebo group as all participants also received the original AREDS formula (or a modified version of it). The study recruited people at high risk of progression to advanced AMD. It concluded that the addition of any combination to the AREDS formulation in the primary analysis did not further reduce risk of progression to advanced AMD.\(^4\)

AREDS2 included a secondary analysis, which showed that lowering the zinc dose and eliminating the beta-carotene had no statistically significant effect on progression to advanced AMD. A post hoc subgroup analysis suggested a benefit of lutein and zeaxanthin given as part of a supplement without beta-carotene. This is of particular interest considering the apparent risks of beta-carotene (see ‘Adverse effects’).\(^4\) After further analysis the authors concluded that ‘the totality of evidence on beneficial and adverse effects from AREDS2 and other studies suggests that lutein/zeaxanthin could be more appropriate than beta carotene in the AREDS-type supplements.’\(^13\) The cautious wording may be appropriate for the strength of the supporting evidence from AREDS2, which was based on secondary analyses rather than the primary outcome.\(^14\)

The NICE Guideline Committee considered the AREDS2 study in their draft guidance. They stated that due to a complicated study design involving a secondary randomisation protocol, the effect of AREDS2 formulation on AMD disease progression is not clear.\(^1\)

### Primary prevention of AMD

A Cochrane review has assessed antioxidant supplements for the prevention of AMD. It concluded that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. The same probably applies to vitamin C and the multivitamin (Centrum Silver) investigated in the one trial reported to date. No evidence was found with respect to other antioxidant supplements, such as lutein and zeaxanthin.\(^15\)

### Adverse effects

There is concern that the high doses of vitamins and minerals contained in many supplements marketed for eye health may cause harm in some people.

- Zinc supplementation causes a small increase in the risk of hospitalisation due to genito-urinary conditions (e.g. urinary tract infection, urinary stones, urinary retention, and prostatic hyperplasia).\(^7\)
- Vitamin E has been linked with an increased risk of heart failure in people with diabetes or vascular disease.\(^16\)
- Beta-carotene has been found to increase the risk of lung cancer in people who smoke or have been exposed to asbestos. Beta-carotene supplements should be avoided in these groups.\(^2,3\)
- The risks of beta-carotene supplements in former smokers are less clear.\(^17\) However, as many studies
suggest that former smokers maintain some increased risk of lung cancer for years after stopping smoking, it is reasonable to expect that beta-carotene may also slightly increase their risk of cancer, at least for a period of several years. In the AREDS2 trial, current smokers or those who had quit smoking less than a year before enrolment were excluded from receiving beta-carotene. Despite this precaution, more lung cancers were noted in the beta-carotene group than the no beta-carotene group, mostly in former smokers.

- Beta-carotene can also cause yellowing of the skin in some people.

NICE were unable to conclude if the treatment benefits of the AREDS formula outweigh the potential risks that could be caused by individual components of the supplement. They recommend further research into the AREDS2 formulation, which does not contain beta-carotene. It has been noted that, at present, clinicians must weigh the potential improved safety of lutein/zeaxanthin over beta-carotene with the lack of long-term information on the safety of lutein/zeaxanthin supplementation.

In their guidance on the secondary prevention of myocardial infarction (MI), NICE make ‘Do Not Do’ recommendations about antioxidant vitamins in those that have had an MI. The guidance states ‘Advise people not to take supplements containing beta-carotene. Do not recommend antioxidant supplements (vitamin E and/or vitamin C) or folic acid to reduce cardiovascular risk.’ The evidence base included data showing that beta-carotene supplementation may increase cardiovascular deaths in those that have had an MI.

A Cochrane review that investigated antioxidant supplements for preventing all cause mortality found no evidence to support their use for primary or secondary prevention. The authors reported that beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A.

### Self-management support

NICE recommend discussing lifestyle advice with people with AMD. Cigarette smoking is the main modifiable risk factor for AMD. It increases the risk of developing AMD two to three-fold. There is likely to be value in smoking cessation interventions to reduce the risk of AMD progression.

Other risk factors for AMD include diet low in omega 3 and 6, vitamins, carotenoid and minerals. The Royal College of Ophthalmologists recommend a diet rich in fruit and vegetables (sources of antioxidant vitamins), oily fish (source of omega-3 fatty acids) and sources of lutein/zeaxanthin (fruit and vegetables and eggs). They note that although these measures are not proven conclusively to be beneficial, they would not be expected to be harmful, and may be useful given what is known about the biology of the retina.

People with AMD should be made aware of sources of practical and emotional support. In addition to any locally available services, ensure that people are aware of The Macular Society (www.macularsociety.org 0300 30301111), who offer a helpline, signposting, local support networks and counselling. The Royal National Institute of Blind People (www.rnib.org.uk 0303 123 9999) and many local organisations also provide advice and support services.

### Advice for people that want to take an antioxidant supplement for AMD

Although vitamin supplements are generally regarded as safe, they may have harmful effects. Clear evidence of benefit is needed before they can be recommended. NICE has reviewed the evidence for antioxidant supplements for AMD. They do not make a recommendation about their use because the current evidence isn't strong enough to do so.

NICE also note safety concerns with some of the ingredients in these supplements. They recommend that further research be undertaken to establish if antioxidant supplements (specifically a formula without beta-carotene) helps slow the progression of AMD.

As the balance of benefits and risks of taking antioxidant supplements for AMD is not currently clear, they are not recommended for prescribing.
Antioxidant supplements marketed for eye health are available for purchase. People that wish to purchase them despite the information above should discuss them with their GP before taking them. They should be made aware of the following:

- The current evidence (which has some important limitations) suggests a benefit of antioxidant supplements in slowing the progression of AMD in those that already have the condition in the following groups of people only:
  - Those with intermediate AMD in at least one eye, or
  - Those with advanced AMD in one eye (but not the other).\(^7,12\)
- Even in these groups any treatment benefit is likely to be modest.\(^7\)
- There is no evidence that these supplements are useful in preventing AMD from developing in the first place.\(^12,15\)
- The ingredients of antioxidant supplements marketed for eye health vary and should be checked carefully. The two supplement combinations that have been studied the most are known as the AREDS and AREDS2 formulas. The AREDS formula includes beta-carotene.\(^7\) The AREDS2 formula replaces beta-carotene with lutein and zeaxanthin (see 'Antioxidant supplements' above for formula details).\(^4\)
- Taking supplements is not risk-free. For example:
  - Beta-carotene has been found to increase the risk of lung cancer in people who smoke or have been exposed to asbestos. People in these groups should not take supplements containing beta-carotene.\(^2,3\) It is advisable for former smokers to avoid beta-carotene supplements too. Some information sources no longer recommend the beta-carotene containing AREDS formula at all.\(^12\)
  - Zinc supplementation can cause a small increase in the risk of admission to hospital due to bladder problems such as urinary tract infection, urinary stones, urinary retention, and prostatic hyperplasia (enlargement of the prostate in men).\(^7\)
  - Vitamin E has been linked with an increased risk of heart failure in people with diabetes or vascular disease.\(^16\)
  - Supplements can sometimes interact with other medication, which the person’s GP will need to consider.

**Costs**

A growing number of antioxidant supplements marketed for eye health are available. Preservision® has a formula that closely resembles the original AREDS formula. Other products, such as MacuLEH Light® and Viteyes 2®, have AREDS2 type formulations. There are also other marketed products, e.g. ICaps®, that contain similar constituents but either in different proportions, or with additional ingredients.

Example costs for some of the more frequently prescribed products are given in Table 1. It should be noted that even if the cost per person is perceived to be small, use across the large potential population could have a significant resource impact.\(^1\)

**Table 1: Example eye health antioxidant supplement prices**

<table>
<thead>
<tr>
<th>Product</th>
<th>Cost per 30 days(^{21})</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICaps® tablets</td>
<td>£9.44</td>
</tr>
<tr>
<td>MacuShield® capsules</td>
<td>£10.95</td>
</tr>
<tr>
<td>MacuLEH Light® tablets</td>
<td>£9.95</td>
</tr>
<tr>
<td>Ocuvite Complete® capsules</td>
<td>£9.42</td>
</tr>
<tr>
<td>Ocuvite Lutein® capsules</td>
<td>£5.50</td>
</tr>
</tbody>
</table>
### Savings

Discontinuing prescribing of antioxidant vitamins marketed for eye health could release savings of over **£1.6 million annually across England and Wales. This equates to savings of £2,874 per 100,000 patients.**

### Summary

Evidence supporting antioxidant supplements in slowing AMD progression comes primarily from two studies, AREDS and AREDS2.\(^4\,^7\) Whilst some of the data suggests a modest benefit, NICE do not consider the evidence to be definitive because of reservations about these studies. There is also concern that the high doses of vitamins and minerals contained in these supplements may cause harm in some people. Further study into antioxidant supplements in AMD is needed before they can be recommended for prescribing.\(^1\) People that wish to purchase these supplements despite this should discuss the matter with their GP before taking them.

### References


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<table>
<thead>
<tr>
<th>Product</th>
<th>Cost per 30 days(^{21})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preservision® tablets</td>
<td>£11.61</td>
</tr>
<tr>
<td>Preservision Original® capsules</td>
<td>£9.89</td>
</tr>
<tr>
<td>Preservision Lutein® capsules</td>
<td>£9.89</td>
</tr>
<tr>
<td>Viteyes 2 Formula® capsules</td>
<td>£11.52</td>
</tr>
<tr>
<td>Viteyes 2 Advanced® capsules</td>
<td>£11.78</td>
</tr>
</tbody>
</table>

10. MIMS Accessed via http://www.mims.co.uk on 09/08/17


Additional PrescQIPP resources

Briefing

Available here: https://www.prescqipp.info/b206-antioxidant-vitamins-for-amd/category/417-antioxidant-vitamins-for-amd

Patient letter

Data pack

Available here: https://basecamp.com/2490352/projects/13770747/todos/300139413#comment_579723273
This resource has been commissioned by NHS Clinical Commissioners on behalf of CCGs in England. Information prepared by Lindsay Wilson, Clinical writer for PrescQIPP CIC, November 2017 and reviewed by Sue Smith, Senior Medicines Evidence Reviewer, November 2017. Non-subscribers who wish to access the implementation resources should contact help@prescqipp.info

Contact help@prescqipp.info with any queries or comments related to the content of this document.

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