## ANTIOXIDANTS AND ZINC FOR ARMD

### Summary of Appraisal

**Date considered by group:**
Thursday 18th September 2008

**Name of Treatment:** generic (trade)
- Ocuvite preservision, Ocuvite lutein, Ocuvite, Viteyes smokers formula plus lutein, Viteyes original formula plus lutein, Icaps plus, Icaps

**Indication(s) for use:**
Prevention of progression of AMD

**Alternative treatments that will be replaced and/or in-year savings that can be realised from elsewhere:**
None / unsure? We do not know if it will prevent patients from requiring lucentis for wet AMD – likely but no estimates. Mr Nick Lee has estimated that it will prevent 1 in 13 patients from requiring PDT:
- Mean cost of treating a patient with PDT over 2 years is £3,206 (NICE TA68).
- Cost of treating 13 patients for 2 years with Ocuvite preservision is £4,680.

**Number of patients a year likely to qualify for treatment:**

<table>
<thead>
<tr>
<th>in Hertfordshire PCTs</th>
<th>In Bedfordshire &amp; Luton PCTs</th>
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<tbody>
<tr>
<td>Mr Nick Lee, Hillingdon NHS Trust, estimates 500-600 patients per million population. Therefore expect between 579 and 695 patients in Hertfordshire.</td>
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**Net Potential annual cost (Cost of treatments – any savings from alternatives or other areas identified for disinvestments):**

<table>
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<th>in Hertfordshire PCTs for year 1:</th>
<th>In Bedfordshire &amp; Luton PCTs</th>
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<tr>
<td>Price of one months treatment of Ocuvite preservision is £15 i.e. £180 per year. NNT:</td>
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<td>- Patients with high risk for developing AMD (categories 3 and 4) = 13 over 5 years (greatest statistical significance)¹</td>
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<td>- Cost to prevent one person with intermediate or advanced AMD progressing is £11,700. Potential annual cost of treating all current patients in Hertfordshire will be between £104k and £125k.</td>
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**Specialist centres involved:**
- Watford General Hospital
- Hillingdon Hospital
- Moorfields Hospital

### RECOMMENDATIONS:

- **A. Strongly recommended for funding.** Development where cost effectiveness is based on firm clinical evidence and is so great compared with current costs of medical care that they ought to be made available at the expense of something else if necessary.

- **B. Recommended.** Developments appear to be cost effective but benefits compared to other treatments and service developments, may be less certain in the light of the quality of evidence.

- **C. Beneficial but high cost.** Developments, which, while demonstrating benefits, are of such high cost or demonstrated only by weak evidence that it is difficult to see how it could be justified in competition of other priorities.

- **D. Not recommended.** Developments where benefits have not been demonstrated.

- **E. Not proven.** Developments where work is in progress but benefits are not yet proven.

- **F. To be piloted.** Developments, which, although benefits may have been proven elsewhere, should be piloted before a final decision is made.
Overall Assessment:
There is limited evidence of efficacy of these products. Most of the evidence for antioxidant eye supplements is based on the AREDS, as other trials are much smaller by comparison. There are concerns about the statistical analysis of this trial as it was originally set up with predefined criteria that did not consider pooling of data for categories 3 and 4. Results should be interpreted with caution. Should antioxidant/zinc supplements be recommended on the basis of the results of this one pooled analysis? We also don’t know the long-term safety (>10 years) of these high-dose vitamin products which are unlicensed and what is best for smokers where there is no evidence for the alternative products. We have no information on the potential benefits from possible reduction in other treatments such as lucentis or PDT by using these products.

Evidence of Clinical Effectiveness:

- A number of observational studies have examined the relationship between AMD and the consumption of antioxidants and zinc. These studies have several limitations, including difficulty in assessing nutrient intake, problems of data collection, and inability to control for confounding factors, which may account for inconsistencies in results. In addition, the low prevalence of AMD, particularly the more advanced stages, in some of these studies limits their ability to detect any modest protective effect.
- Several observational studies have found no association between antioxidant and zinc intake and AMD. These include:
  - The Beaver Dam Eye study
  - Blue Mountains Eye study
  - Women’s Health Initiative study
- Several randomised controlled trials have investigated the effect of dietary supplements on the development and progression of AMD. The most frequently cited study is the Age-Related Eye Disease Study (AREDS):
  - Researchers reported outcomes for three baseline categories of participants (3,640 patients) with early or borderline AMD features, intermediate AMD or with advanced (dry or wet) AMD or reduced visual acuity due to AMD in one eye.
  - The trial was randomised, double blind, and compared to placebo.
  - Follow up was for a mean of 6.3 years (minimum 5 years)
  - Patients were assigned to the following categories; category 1 (typically free from AMD features), category 2 (mild or borderline AMD features in one or both eyes), category 3 (absence of advanced AMD in both eyes with at least visual acuity of 20/32 and 1 large drusen in one eye that did not involve the centre of the eye) and category 4 (features of advanced AMD in one eye only).
  - Two primary outcomes – progression to advanced AMD and reduction in visual acuity (≥15-letter decrease).
  - Overall, there was a statistically significant odds reduction for the progression to advanced AMD in patients treated with antioxidants plus zinc compared to placebo (OR 0.72; 99% CI 0.52 to 0.98).
  - In the early AMD group. Only 1.3% of patients (12 in the treatment arms and 3 in the placebo arm) developed advanced AMD by year 5. This was a much lower rate than the researchers had expected so they conducted a post-hoc analysis excluding this group. The analysis of subjects with more severe disease showed a greater reduction in risk of progression of AMD, with ORs for antioxidants plus zinc being statistically significant (OR 0.76; 99% CI 0.55 to 0.91). These results must be interpreted cautiously as the study was not powered for this analysis.
  - Again this analysis was underpowered.

- Limitations of AREDS:
  - Originally set up with predefined criteria that did not consider pooling of data for categories 3 and 4. Therefore underpowered to detect any difference between these groups of patients.
  - 67% of participants also took Centrum.
  - The population in the study were relatively well nourished and may differ from the general population.
  - Retinal outcomes were based on colour fundus photography, not on fluorescein angiography or clinical examinations.
  - It is unknown how long patients at risk for AMD should use supplements.
  - Did not account for possible genetic component of disease.
  - Long-term safety and efficacy of these supplements is unknown.

Safety Issues:
- Only AREDS has examined the safety of supplements in any detail. It provides some reassurance about the safety of high-dose zinc and antioxidants used for six years.
- The incidence of adverse effects was not statistically different between groups but patients taking zinc had increased hospital admissions for genitourinary symptoms and patients reported yellowing of the skin associated with beta-carotene (NNH of 40). However, the safety of some of the components of the AREDS supplements has been questioned in other studies.
- While AREDS was ongoing, it became evident from other studies that beta-carotene was associated with a higher incidence of lung cancer in smokers.
- High dose vitamin E supplements may increase the risk of cardiovascular problems in those with any form of CVD and has implications for those taking warfarin as well as problems with zinc causing anaemia.

Cost & Comparative health economic evidence
- None

Needs of the population
How important is this treatment in the prevention of AMD? Will it prevent or reduce the use of other therapies e.g. lucentis, PDT for AMD? Should there be a difference in the treatment of dry or wet AMD?

Needs of the community

Potentially a £104k-£125k per year spend on an unlicensed product. Could this be used for other therapies which are licensed, NICE approved, and have better outcomes?

Reviewer’s assessment:

For patients who do not have AMD or who have early disease, there is no evidence from randomised controlled trials to support the use of nutritional supplements. It would seem reasonable to advise people without AMD or with only mild signs of the disease to follow Department of Health dietary guidelines and increase consumption of fruit and vegetables.

For patients with intermediate or advanced AMD in one eye, there is limited evidence from one study (AREDS). However, it must be noted that this study was originally set up with predefined criteria that did not consider pooling of data for categories 3 and 4. Therefore underpowered to detect any difference between these groups of patients.

Products available in the UK that most closely match this combination are PreserVision and Viteyes Original. Similar formulations where the beta-carotene has been substituted with lutein lack the evidence base of the orginal formulation.

All of these supplements are not licensed medicinal products and so they have not undergone regulatory assessment.

They contain doses that are significantly higher then recommended daily allowances and the safety profile long-term is not known.

EFFECTIVENESS RATING INFORMATION

Grading of Evidence:

Outcome:

References:


AMD Eligibility Categories (from AREDS trial)

<table>
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<tr>
<th>AMD Category</th>
<th>First Eye*</th>
<th>Pigment Abnormalities^</th>
<th>Second Eye</th>
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<tr>
<td>Drusen Size^</td>
<td>Drusen Area^</td>
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<tr>
<td>1 None or small (&lt;63µm)</td>
<td>&lt;125µm diameter circle (~5-15 small drusen)</td>
<td>None</td>
<td>Same as first eye</td>
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<td>2 Small (&lt;63µm)</td>
<td>≥125µm diameter circle (about 1/150 disc area)</td>
<td>Absent or present, but GA absent</td>
<td>Same as first eye or Category 1</td>
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<tr>
<td>Or intermediate (≥63, &lt;125µm)</td>
<td>At least 1 druse</td>
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<tr>
<td>Or none required if pigment abnormalities are present</td>
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<tr>
<td>3a Intermediate (≥63, &lt;125µm)</td>
<td>≥360µm diameter circle 9about 1/16 disc area) if soft indistinct drusen are present (~20 intermediate drusen)</td>
<td>Absent or present, but central GA absent</td>
<td>Same as first eye or Category 1 or 2</td>
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<td>Or large (≥125µm)</td>
<td>≥656µm diameter circle (about 1/5 disc area), if soft indistinct drusen are absent (~65 intermediate drusen)</td>
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<td></td>
<td>Or none required, if noncentral GA* is present</td>
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<tr>
<td><strong>3b</strong></td>
<td>First eye same as Category 3a</td>
<td></td>
<td>VA&lt;20/32 not due to AMD* or uniocular disqualifying disorder is present£</td>
</tr>
<tr>
<td><strong>4a</strong></td>
<td>First eye same as Category 1, 2, or 3a</td>
<td></td>
<td>Advanced AMD¶</td>
</tr>
<tr>
<td><strong>4b</strong></td>
<td>First eye same as Category 1, 2, or 3a</td>
<td></td>
<td>VA&lt;20/32 due to AMD, but advanced AMD¶ not present§</td>
</tr>
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*Must have visual acuity (VA)≥20/32, no advanced age-related macular degeneration (AMD), and no qualifying lesions

*Drusen and geographic atrophy (GA) are assessed within 2 disc diameters (3000µm) of the centre of the macula

*Pigment abnormalities (increased pigmentation or depigmentation) within 1 disc diameter of the centre of the macula

*Eye not eligible for VA event

*Eye not eligible for AMD event

*The GA involving centre of macula or signs of choroidal neovascularisation (presence beneath the retinal pigment epithelium or sensory retina of fluid, blood, or fibrovascular or fibrous tissue
Comments from Various Medical Papers and Opinions from Specialists

• Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration – Evans JR Cochrane Database of Systemic Reviews 2006 Issue 2
  o Authors’ conclusions - the evidence as to the effectiveness of antioxidant vitamin and mineral supplementation in halting the progression of AMD comes mainly from one large trial in the USA. The generalisability of these findings to other populations with different nutritional status is not known. Further large, well-conducted randomised controlled trials in other populations are required. Long-term harm from supplementation cannot be ruled out. Beta-carotene has been found to increase the risk of lung cancer in smokers; vitamin E has been associated with an increased risk of heart failure in people with vascular disease or diabetes.
  o Methodological quality – in AREDS four people were documented as being unmasked to study group. More people in the antioxidant group (8.3%) reported changes in skin colour (yellowing) than in the placebo group (6.0%, P<0.01) and more people in the zinc groups reported difficulty swallowing the study tablets (17.8% versus 15.3%, P=0.04).
  o Adverse effects – participants in the zinc arms reported more anaemia (13.2% versus 10.2%, P=0.004), however, serum hematocrit levels were the same. They found that participants taking zinc had a lower mortality. Later follow-up of the cohort of people taking part found that there was a significant increase in hospital admissions due to genitourinary diseases in people taking zinc supplements (11.1% versus 7.6%, P=0.0003).

• AMD Interim Guidelines- version 3; The Royal College of Ophthalmologists Interim Recommendations for the Management of Patients with Age-related Macular Degeneration (AMD)
  o Dry AMD:
    ➢ There is, unfortunately, no medical or surgical treatment currently available for dry AMD. However patients can be helped by supportive measures such as low vision assessment, provision of and advice on the use of optical aids and counselling about the condition and prognosis. Smoking is a recognised risk factor for both dry and wet AMD. Ocular nutritional supplements have been shown (in the AREDS Study) to slow the progression of dry AMD to more advanced stages. Such nutritional supplements should therefore be recommended to patients. Patients should be advised to avoid smoking.

• Hillingdon Medicines Management Committee
  o Have only approved ocuvite preservision for patients with advanced age-related macular degeneration in one eye only (Category 4) for non-smoking patients; it did not extend to the preparation for smokers i.e. Ocuvite Lutein. Mr Nick Lee convinced the committee members that GPs should be allowed to continue the prescribing.
  o GPs will only prescribe on the written recommendation of Mr Nick Lee or other eye specialists.
  o Mr Nick Lee supplies patients with a sample pack as the pharmacy do not stock this product.
  o Hillingdon PCT took the view that if a GP wanted to prescribe it, they could go ahead, but they would remind them that there was only one published study to show any benefit in AMD patients. They also explained that it is available OTC and has no specific license for AMD patients.

• Comments from Mr Nick Lee (Hillingdon Hospital) via personal communication:
  o Patients are stopped when their vision is below 6/96 i.e. they have advanced AMD
  o Uses preparations for AREDS Category 3 and 4
  o Treats smokers
  o Feels that almost 100% of patients are compliant with this (note: at five year follow up 71% of participants were taking 75% or more of their tablets in AREDS and that this was a well followed-up RCT; patients need to take four tablets per day)

• Comments from Mr Adnan Tufail (Moorfields Hospital) via personal communication:
  o Only uses preparations for AREDS Category 4
  o Does not treat smokers

• Comments from Royal Free Hospital Pharmacy:
  o These preparations and use in AMD has not been considered by the trust