**Vitamins to Reduce the Risk of Progression in Age-Related Macular Degeneration**

**(Overview of AREDS2 Research Group Findings)**

**December, 2013**

Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives

and Ophthalmology Field Advisory Committee

The AREDS2 Research Group designed a study to evaluate a few outstanding questions with regards to the use of vitamins in preventing the progression of age-related macular degeneration (ARMD). The first question was to test whether adding antioxidants (lutein and zeaxanthin), omega-3 fatty acids (DHA and EPA) or both antioxidants and omega-3 fatty acids might further reduce the progression to advanced ARMD compared to the original AREDS supplement. The original AREDS supplement consisted of vitamin C 500mg, vitamin E 400 IU, beta carotene 15 mg, zinc oxide 80 mg and copper 2 mg. The second question was to test if eliminating beta carotene and reducing the zinc dose made any impact on ARMD progression.

A brief summary of the trial is provided. For details, please refer to the actual trial referenced here.

Adult patients (aged 50-85 years) at high risk of ARMD progression with either bilateral large drusen or large drusen in one eye plus advanced ARMD (neovascular or central geographic atrophy) in the other eye were included. Evaluations included annual eye exam including visual acuity assessment, and anatomic evaluations to assess for ARMD. Adherence was assessed via pill count and blood was drawn to measure serum levels of lipids, lutein + zeaxanthin, fat-soluble vitamins, zinc and copper at baseline and at 1, 3 and 5 years. Follow up visits were scheduled annually until November 2012 for a median of 5 years.

In a phase III, multicenter, randomized fashion, patients were placed in either of the following primary randomization arms:

1. Placebo (AREDS supplement, no true placebo)
2. AREDS with Lutein 10 mg + zeaxanthin 2 mg
3. AREDS with DHA 350 mg + EPA 650 mg
4. AREDS with Lutein + zeaxanthin and DHA + EPA

Those consenting to participate in the secondary randomization\* received one of the following formulations:

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| --- | --- | --- | --- | --- | --- |
| Formulations | Vit C (mg) | Vit E (IU) | Beta carotene (mg) | Zinc oxide (mg) | Copper (mg) |
| 1 | 500 | 400 | 15 | 80 | 2 |
| 2 | 500 | 400 | 0 | 80 | 2 |
| 3 | 500 | 400 | 15 | 25 | 2 |
| 4 | 500 | 400 | 0 | 25 | 2 |

\* Current or former smokers who stopped smoking within the year before enrollment were randomly assigned to Formulations # 2 or 4 (without beta carotene).

The primary outcome was to compare 3 active treatment arms with placebo (AREDS vitamin) on progression to advanced ARMD. Multiple secondary outcomes were evaluated, but not all findings are reported here. Please refer to the original study for further details. Secondary outcomes included:

1. Progression to moderate vision loss (> 15 letter loss)
2. Progression of lens opacity based on photo or incidence of cataract surgery
3. Moderate vision loss or improvement in participants with advanced ARMD
4. Effect of eliminating beta carotene from original AREDS formulation on ARMD progression
5. Effect of reducing zinc from 80 mg to 25 mg on ARMD progression
6. Effect of eliminating beta carotene from original AREDS formulation on moderate vision loss
7. Effect of reducing zinc in original AREDS formulation on moderate vision loss

Results: A total of 4203 patients were randomized from 82 clinical sites (4188 included in primary randomization; 3036 included in secondary randomization). The median follow up was 4.9 years (range, 4.3 – 5.1 yrs). Some baseline characteristics of the study population include: 97% Caucasian, 57% female; median age 74 years; 7% current smokers; 49% former smokers. Lens characteristics include: 69% phakic, both eyes; 6.7% pseudophakic/aphakic in one eye; 25% pseudophakic/aphakic in both eyes; 56% had > 1 eye without cortical opacity; 71% had > 1 eye without posterior subcapsular opacity.

Efficacy results of the primary randomization arms:

|  |  |  |
| --- | --- | --- |
| **Arms** | **Probability of progression to advanced ARMD** | **Comparison to placebo (AREDS vitamin formulation)** |
| Placebo (AREDS supplement, no true placebo) | 31% (493 eyes [399 subjects]) | \*\*\* |
| Lutein / zeaxanthin (10 mg/ 2 mg) | 29% (468 eyes [399 subjects]) | HR 0.90 [98.7% CI, 0.76-1.07]; p=0.12 |
| DHA plus EPA (350 mg/ 650 mg) | 31% (507 eyes [416 subjects]) | HR 0.97 [98.7% CI, 0.82-1.16]; p=0.70 |
| Lutein /zeaxanthin and DHA plus EPA | 30% (472 eyes [387 subjects]) | HR 0.89 [98.7% CI, 0.75-1.06]; p=0.10 |

Efficacy results of the secondary randomization arms:

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| --- | --- | --- | --- | --- | --- | --- |
| **Formulations** | **Vit C (mg)** | **Vit E (IU)** | **Beta carotene (mg)** | **Zinc oxide (mg)** | **Copper (mg)** | **HR [95% CI]; p value** |
| 1 | 500 | 400 | 15 | 80 | 2 | \*\*\* |
| 2 | 500 | 400 | 0 | 80 | 2 | \*\*\* |
| 3 | 500 | 400 | 15 | 25 | 2 | 1.06 [0.95-1.19]; P=0.32 |
| 4 | 500 | 400 | 0 | 25 | 2 | 1.07 [0.94-1.20]; P=0.31 |

A subgroup analysis was performed to determine if supplemental lutein + zeaxanthin vs. no supplemental lutein + zeaxanthin given to patients with various levels of dietary intake of lutein + zeaxanthin could impact ARMD progression. The findings indicate that patients in the group with the lowest dietary intake benefited most from the addition of these antioxidants [HR 0.74(95% CI, 0.59-0.94); p=0.01].

Points with regard to safety results:

* There were no differences in serious adverse events across groups in the primary randomization
* Secondary randomization noted more lung cancers in the beta carotene group [23 (2%) vs. 11 (0.9%); nominal P=0.04]. Thirty-one (91%) who developed lung cancers were former smokers. Former smokers were defined as those not smoking for 1 year or greater.
* Dietary supplementation had no statistically significant effect on mortality
* No differences for low-dose vs. high-dose zinc effect
* No differences for beta carotene vs. no beta carotene effect

So, some basic points for the overall conclusion of this trial can be made:

* In patients at high risk for progression to advanced ARMD, daily supplement of lutein + zeaxanthin, DHA + EPA or lutein + zeaxanthin and DHA + EPA provided no statistically significant effect on progression to advanced ARMD or changes in visual acuity.
* There were no beneficial or harmful effects of DHA + EPA in the treatment of ARMD.
* Serum levels of lutein + zeaxanthin were lower in those receiving beta carotene, supporting the literature suggesting that there is competitive absorption between the carotenoids.
* A higher incidence of lung cancer was noted in former smokers who took the beta carotene product.
* No apparent effect on vision noted by eliminating beta carotene and reducing zinc content.
* Patients who took supplemental lutein + zeaxanthin, particularly those with low dietary intake, were less likely to progress to advanced ARMD compared to those who did not take the supplements.

**Pertinent Points with Regard to Vitamin Products**

Before the AREDS2 study results were released, Bausch & Lomb anticipated the results and marketed a product called “AREDS 2 Formula with Lutein 10mg & Omega-3 FAs 1000mg” in a soft gel formulation. This product has been discontinued since the AREDS2 study results showed no benefit to providing Omega-3 FAs. A new formulation has replaced this product. This new product is called simply “AREDS 2 Formula” and is provided as a soft gel. It contains the formula supported by the AREDS2 study.

**Moving Forward**

As a result of the AREDS2 study findings, the MAP-VPE-PBM voted to remove beta carotene-containing eye vitamins from the VA National Formulary.

Effective 12/9/2013, the new AREDS 2 Formula vitamin will be on FSS contract. PreserVision + Lutein remains on FSS contract until 7/12/2014. The chart below compares the two products. Of note, PreserVision + Lutein does not contain zeaxanthin.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Product** | **C (mg)** | **E (IU)** | **Zn (mg)** | **Cu (mg)** | **EPA (mg)** | **DHA (mg)** | **L (mg)** | **Z (mg)** | **B-carotene** |
| AREDS2 Formula | 500 | 400 | 80 | 2 | 0 | 0 | 10 | 2 | 0 |
| PreserVision + Lutein | 452 | 400 | 69.6 | 1.6 | 0 | 0 | 10 | 0 | 0 |

**References:**

AREDS2 Research Group. Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration. The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial. JAMA 2013; 309 (19): doi: 10.1001/jama.2013.4997.

Chew EY, Clemons TE, Agron E, et al. Long-Term Effects of Vitamins C and E, Beta Carotene and Zinc on Age-related Macular Degeneration. AREDS Report No. 35. Ophthalmology 2013; 120: 1604-1611.