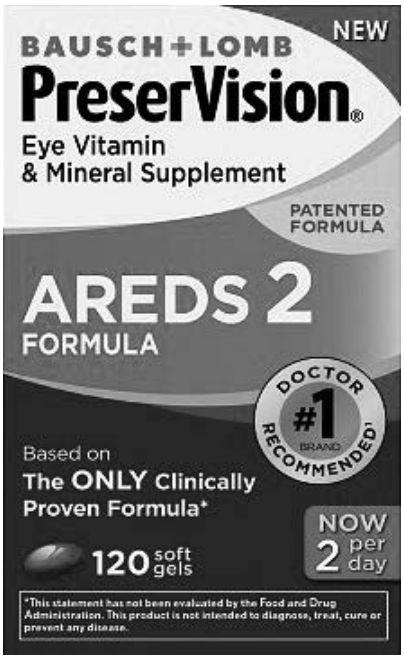
Vitamins and Age-Related Macular Degeneration

Comments and Opinions from the
Retina Service at the Emory Eye Center
Based on: Age-Related Eye Disease Study AREDS[1] and AREDS2[2,3]
and other published data: Updated January 2014

SUMMARY: If you or someone you know has Age-related Macular Degeneration (AMD), you should be aware of an important study called the Age-Related Eye Disease Study (AREDS) and the recently released AREDS2. AREDS demonstrated the beneficial effect of antioxidants (Vitamin C, E, beta-carotene and zinc-copper) and demonstrated a delay in progression of AMD. AREDS2 data have demonstrated that the addition of Lutein (10 mg) and Zeaxanthin (2 mg) should replace the beta-carotene component. Caution was raised, *in smokers or former smokers*, that use of beta-carotene was *associated with a higher rate of lung cancer*. AREDS2 *did not show any significant benefit with the additional use of omega-3* (DHA/EPA) supplements. Furthermore, there was no effect of these supplements on the rate of cataract progression.

- An Ophthalmologist should examine those over age 50 or with a family history of AMD to determine their risk for progression, such as those who are "at risk".
- There is no conclusive data that taking supplements earlier is beneficial.
- Individuals "at risk" (according to AREDS criteria) should consider using these supplements.
- Zinc may increase the risk of genitourinary complications.
- Individuals taking cholesterol or lipid-modifying medications should consult their physician (see #11 on page 3).



WE CURRENTLY RECOMMEND
Note: We do not have a financial interest in this nutritional product.

OCUVITE PRESERVISION (or an equivalent)
One gel capsule in the AM and one in the PM with food
PLUS

CENTRUM SILVER (or multivitamin of your choice)

IMPORTANT CONCEPT: A vitamin pill is no substitute for a **healthy lifestyle**: In fact, it is estimated that by modifying one's lifestyle, there may be up to a 70% reduction odds for early AMD:

- **DON'T SMOKE!**
- **Consume a low-fat diet**
- **Eat plenty of fresh fruits and especially green leafy vegetables, & nuts**
- **Regular exercise (walking, cycling, swimming, etc.)**
- **Wearing sunglasses and/or hat to protect against chronic sun exposure.**

KEY AGENTS (2 capsules/day):

Antioxidants:	Vitamin C	500 mg	
	Vitamin E	400 IU	
	Lutein	10 mg	***SMOKERS/Former smokers: AVOID Beta Carotene***
	Zeaxanthin	2 mg	
Zinc + Copper:		25 to 80 mg zinc oxide + 2 mg of copper	

Other Common Questions about the AREDS Study

1) What is AMD?

Age-related macular degeneration is an aging change in the back of the eye that may lead to loss of the central vision. AMD is the leading cause of "legal blindness" in the industrialized world in individuals over age 50. The early stages are extremely common. The eye is like a camera, and the retina is the film in the back of the camera. The macula forms the center of the film, much like the bulls-eye of a dartboard. Yellow deposits or drusen form under the macula as we age. Drusen are common, and they have many shapes and sizes. The AREDS categorized and counted drusen to determine the effects of vitamin therapy on macular degeneration. Furthermore, AREDS clearly defined the "at risk" group who benefited from treatment.

2) What should I do if I may have AMD?

Contact your ophthalmologist to determine whether you have AMD, and if so, what category or stages of drusen are present. The ophthalmologist will examine the back of your eye using dilating drops to check for drusen or other changes. They will then provide you with an assessment of your individual risk based on many findings from the history and exam.

3) What was the beneficial effect for those with certain types of drusen?

Beneficial effect was classified as either a decrease in the progression to advanced AMD *or* less progression of vision loss from AMD. For the intermediate level of drusen, the risk of reduction in progression to advanced AMD in those taking antioxidants plus zinc compared with placebo was 20-30%. The reduction in progression to advanced AMD is also reflected in visual acuity.

4) What should individuals do who have "mild" or small drusen?

Current recommendations are to defer consideration of the specialized supplementation used in this trial until the risk of progression is higher. There is no evidence from the AREDS Study at this time that the supplements decrease the rate of progression from early stages of AMD to the "at risk" level. Some may suggest that this study provides "Proof of Principle" in favor of using antioxidant vitamins at earlier stages, thus taking vitamins could be beneficial for decreasing progression "at risk" AMD. AREDS does not support this concept. AREDS is the first study to demonstrate that a relatively safe systemic therapy effectively decreases progression of "at risk" AMD. A "neutral" recommendation for the use of antioxidant therapy in earlier stages is warranted at this time.

5) Should I continue taking a Multivitamin in addition to the special supplement?

All patients took a vitamin pill twice daily of identical size, shape and color. The placebo group's vitamin did not contain antioxidants or zinc. However, in all groups (including placebo controls), patients were allowed to take a **Centrum** multivitamin.

6) Were blood tests used to document systemic levels of antioxidants?

In AREDS, four clinical centers collected baseline samples for various antioxidants plus total cholesterol, high-density lipoproteins, triglycerides, lutein, zeaxanthin, lycopene and cryptoxanthin. Three centers continued to collect samples annually. Hematocrit was also measured regularly at all centers. No significant anemia or blood lipid changes were found. In AREDS2, baseline serum levels were both balanced and monitored.

7) Were there safety issues involved with the use of antioxidants and/or zinc?

In AREDS, individuals on zinc therapy were slightly more prone to urinary tract infections (not found in AREDS 2), prostatic hyperplasia (in men) and stress incontinence (in women). Based on the harmful effects of beta-carotene associated with smokers, participants who were *current or former* smokers were given the opportunity to be assigned to a study medication that excluded the antioxidant component because of the association reported with lung cancer. For these reasons, **people who smoke cigarettes should *avoid taking the beta-carotene* component of the antioxidants**. In 2004 AREDS report #13[4] reported lower mortality for those on zinc supplements than those not taking zinc (suggesting a protective effect that remains unexplained for those on zinc). More data is required to investigate this unexpected finding. In AREDS2, former smokers had a significantly higher rate for development of lung cancer when using beta-carotene. Therefore, supports the recommendation to avoid this component in smokers or former smokers.

8) Were there minor side effects or complications?

In AREDS, individuals who took antioxidant vitamins had a higher incident of "yellow skin." Individuals in the antioxidant group had *less frequent* "circulatory" events than the placebo group.

9) What is the impact of Lutein and Zeaxanthin based on the AREDS results?

Lutein (10 mg), zeaxanthin (2 mg) or L/Z, was specifically studied in AREDS2. L/Z are the predominant carotenoids (yellow pigment) in the human macula. AREDS2 data suggests L/Z should be used to substitute for the beta-carotene used in the original formulation. Yellow pigments acts as a filter to the shorter wavelength, higher energy blue light and have anti-oxidant properties. Centrum includes Lutein in the formulation, and lutein is found naturally in many vegetables, possibly the best source of these compounds (See #13 below).

10) Are there criticisms of the AREDS Study?

The power of the study is supported by a large number of participants: AREDS = 3640; AREDS2 = 4203, yet subgroup analysis breaks down into smaller groups that have less statistical significance. Many trends that did show a significant treatment benefit will require further study.

11) What other associations of supplementation with medical conditions should we be aware? What about serum cholesterol, lipids, aspirin use or progression of Alzhiemer's Disease?

Brown and colleagues[5] examined patients with coronary artery disease and low levels of high-density lipoprotein (HDL or "good cholesterol") were treated with one of four treatment groups: simvastatin plus niacin, antioxidants, simvastatin plus niacin plus antioxidants, or placebo. They found that the protective effect of increasing HDL cholesterol *was attenuated (or less effective) by concurrent therapy with antioxidants*. While the dosages of antioxidants were higher (Vit. E 800 IU, Vit. C 1000 mg, Beta-carotene 25 mg, and selenium 100 mg.), the use of antioxidants in this setting requires further patient education.

There is discussion[6] that cerebral zinc may play a role in the evolution of Alzheimer's disease. Recent reviews[7] have reached inconclusive recommendations on this association. In fact too little may promote more rapid aging and mental decline, too much may also be harmful. AREDS2 demonstrated that the lower zinc dose was equally effective; therefore, lower zinc intake is acceptable. Hyperzincemia has also been suggested to aggravate glucose intolerance in non-insulin dependent diabetics.[8]

Recent observational studies have indicated a possible link between aspirin use and AMD. The Beaver Dam Eye Study reported two times the incidence of late macular degeneration in patients who used aspirin at least twice weekly for 10 years compared to those who used no aspirin.[9] It is important to understand that this result does not implicate aspirin as a *cause* of AMD. Such observational studies do not have the ability to show cause and effect, but may simply show a *possible* association. Other studies have shown a potential protective effect of aspirin against the development of AMD.[10] In light of all of the available information on the subject of aspirin use and AMD, we currently recommend that those patients who have been instructed to use aspirin by a physician continue their aspirin therapy as prescribed.

12) I have heard that higher dosages of Vitamin E are harmful.

Miller and colleagues[11] performed a large-scale analysis of individuals taking Vitamin E, pooling results from 19 clinical trials, approximately 136,000 people total. They found that that those who took higher dosages of Vitamin E (>400 IU) had more deaths than those who used less Vitamin E: 39 deaths per 10,000 in higher dose vs. 19 deaths per 10,000 in the lower dose (a significant difference). Experts from the AREDS trial have indicated that in the AREDS Study, there was no increase in mortality in those on 400-450 IU of Vitamin E in the trial.[12] The addition of a multivitamin (Centrum) with the AREDS supplement increases the Vitamin E levels by approximately 45 IU for a total of 445 IU. This study indicates caution with higher levels of Vitamin E (again, more is not always better!). We feel that 445 IU is safe in the setting of level 3 or 4 AREDS AMD, but ***additional vitamin E supplementation should be avoided***.

13) Are there other studies that support some of the AREDS findings?

Researchers from Denmark[13] examined 68 trials that compared various anti-oxidants in "low-bias-risk" studies (including nearly 181,000 participants). They found:

- Taking vitamin A supplements increased the risk of death by 16 percent
- **Taking beta-carotene supplements increased the risk of death by 7 percent
- Taking vitamin E supplements increased the risk of death by 4 percent (see #12 above)
- Taking vitamin C supplements did not have any effect on risk of death
- Selenium may have a beneficial effect on longevity

EMORY RETINA SERVICE:

Timothy W. Olsen MD
G. Baker Hubbard III, MD
Jiong Yan, MD
Chris Bergstrom MD
Blaine Cribbs MD
Steven Yeh MD
Andrew Hendrick MD
Purnima Patel MD
Josh Robinson MD

REFERENCES AND UPDATES AVAILABLE UPON REQUEST:

http://www.eyecenter.emory.edu/eye_conditions/macular_degeneration.htm

EMORY
EYE CENTER

REFERENCES

1. A randomized, 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: AREDS report no. 8. *Arch Ophthalmol*. Oct 2001;119(10):1417-1436.
2. The Age-Related Eye Disease Study 2 Research G, Chew EY, Clemons TE, et al. Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression: AREDS2 Report No. 3. *JAMA ophthalmology*. Dec 5 2013.
3. Age-Related Eye Disease Study 2 Research G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. May 15 2013;309(19):2005-2015.
4. Clemons TE, Kurinij N, Sperduto RD. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS Report No. 13. *Arch Ophthalmol*. May 2004;122(5):716-726.
5. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. Nov 29 2001;345(22):1583-1592.
6. Kaiser J. Alzheimer's: could there be a zinc link? *Science*. Sep 2 1994;265(5177):1365.
7. Exley C. Aluminium and iron, but neither copper nor zinc, are key to the precipitation of beta-sheets of Abeta_{42} in senile plaque cores in Alzheimer's disease. *J Alzheimers Dis*. Nov 2006;10(2-3):173-177.
8. Raz I, Karsai D, Katz M. The influence of zinc supplementation on glucose homeostasis in NIDDM. *Diabetes Res*. Jun 1989;11(2):73-79.
9. Klein BE, Howard KP, Gangnon RE, Dreyer JO, Lee KE, Klein R. Long-term use of aspirin and age-related macular degeneration. *JAMA*. Dec 19 2012;308(23):2469-2478.
10. Christen WG, Glynn RJ, Ajani UA, et al. Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians. *Arch Ophthalmol*. Aug 2001;119(8):1143-1149.
11. Miller ER, 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. Jan 4 2005;142(1):37-46.
12. Chew EY, Clemons T. Vitamin E and the age-related eye disease study supplementation for age-related macular degeneration. *Arch Ophthalmol*. Mar 2005;123(3):395-396.
13. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention: Systematic Review and Meta-analysis. *Jama*. Feb 28 2007;297(8):842-857.