

National PBM Drug Monograph

Ocuvite PreserVision ®
VHA Pharmacy Benefits Management Strategic Healthcare Group
and Medical Advisory Panel
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Introduction^{1,2}

Age-related macular degeneration (AMD) is one of the most common causes of visual impairment and loss of central vision in patients 65 years of age and older. It is a degenerative disorder of the retinal pigment epithelium (RPE) characterized by development of deposits known as drusen. Patients are grouped into categories based on ophthalmoscopic findings. There is also a wet form of AMD characterized by an exudative process resulting in scarring. This form of AMD accounts for approximately 15% of cases and the majority of severe vision loss due to AMD. Risk factors for AMD include older age, race (Caucasian), female gender, family history, light-colored iris, cardiovascular disease, smoking, and hypertension. There is no known effective prophylaxis for AMD, and there is no effective treatment for most cases of AMD. Various trials have investigated the use of nutritional supplements in AMD prevention and treatment. The results of these trials have been mixed and are complicated by the duration of many of the trials. A trial of 4-5 years may not be sufficient to document the impact of the age related changes in AMD. Investigations have included vitamin E, zinc and antioxidants³⁻⁵. A Cochrane review has made the recommendation that healthy people should not take supplements to prevent the onset of AMD. Patients with stage 3 or 4 AMD may benefit from supplements and this will be discussed further in the monograph.^{6,7} One of the supplements studied in AMD is Ocuvite PreserVision® which contains vitamins A, C, E, zinc and copper.

Pharmacology/Pharmacokinetics⁸

The components for this agent were selected based primarily on their potential role as antioxidants. Vitamin A has functions in the conjunctiva, retina and cornea. Prolonged diets low in beta-carotene have been linked to AMD. Zinc was added due to high concentration of it in the RPE. AMD may be linked to its deficiency and the loss of zinc dependent coenzymes. Copper was added to prevent zinc induced copper deficiency.

Since this supplement is not an agent approved by the FDA there have been no direct studies of its pharmacokinetic parameters. The following discussions will relate to the components of Ocuvite PreserVision®. The majority of the product is absorbed in the GI tract, with vitamin E requiring fat for its absorption. Zinc absorption may be impacted with food products containing bran or phylates. Vitamin A is predominately stored in the liver while the other components of the agent are widely distributed to other body tissues. Copper and zinc are excreted primarily in the stool and bile, vitamin C and E in the urine and approximately 10% of unchanged vitamin A in the feces.

FDA Approved Indication(s) and Off-label Uses⁹

Ocuvite PreserVision® provides nutritional supplementation for the health of the eyes. Even though Ocuvite PreserVision® has been shown to reduce the risk of vision loss from AMD in the Age-Related Eye Disease Study (AREDS) conducted by the National Eye Institute, this product is a nutritional supplement and has not been evaluated by the FDA. It is not intended to diagnose, treat, cure or prevent any disease. Additionally, there are many caveats to the AREDS study that should be considered before deciding on therapy.

Current VA National Formulary Status

Similar drugs currently on VANF include; multiple vitamins both with and without minerals and oral formulations of vitamin A,C or E.

Dosage and Administration⁹

The recommended adult dose is two tablets twice daily. The product should be taken with meals to avoid nausea. If given with prescription medications the patient should be screened for the possibility of interactions with those medications.

Adverse Effects (Safety Data)^{8,9}

The long-term safety of high dose supplementation with these agents is unknown. The AREDS trial followed patients for 5 years; safety beyond that point is not known. Previous trials have suggested Vitamin A (beta-carotene) might be harmful in smokers and lead to an increased cancer risk. Additionally, alcohol consumption may be associated with an increased risk of adverse effects. There is also concern that long-term use of vitamin A in high doses (> 5,000 IU a day) can increase the risk of osteoporosis in women. Vitamin C & E do not have proven harmful effects that we know of but there has been some data that suggest that they interfere with effectiveness of statin therapy.¹⁴ Elevated levels of zinc have been associated with neurodegeneration in animal models, elevation of glycosylated hemoglobin levels in type 1 diabetics, decreased glucose tolerance in type 2 diabetes and elevated serum zinc levels may be found in patients with Alzheimer's disease.

Precautions/Contraindications^{8,9}

Copper should be avoided in patients with biliary tract obstruction or Wilson's disease. The risks of high dose nutritional supplements are not known. Patients with chronic diseases such as, cancer, heart disease and diabetes should use these preparations with caution.

Drug Interactions^{8,9}

- Warfarin: increased hypoprothrombinemic effect occurs with high doses of vitamin A or high doses of vitamin E (>400 IU). Vitamin C can reduce the anticoagulant action of warfarin.
- Iron: iron interferes with the absorption of vitamin E. Absorption of iron increases with co-administration of vitamin C.
- Isotretinoin: concurrent use may increase the risk of vitamin A toxicity.
- Vitamin C: acidifies urine resulting in reabsorption of acidic drugs and an increase in the excretion of basic drugs from the renal tubules (unknown clinical relevance).
- Tetracycline and fluoroquinolones: zinc decreases the absorption of tetracycline and fluoroquinolones.
- Copper: absorption of copper is decreased by concurrent use of high doses of zinc or vitamin C.

Clinical Trials¹¹

Citation	Age-Related Eye Disease Study Research Group. 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. <i>Arch Ophthalmol</i> 2001;119:1417-1436.
Study goals	<ul style="list-style-type: none"> To assess the clinical course, prognosis, and risk factors for AMD To evaluate the effects of high doses of antioxidants and zinc on the progression of AMD and vision loss
Criteria	<p><u>Inclusion:</u></p> <ul style="list-style-type: none"> Patients aged 55–80 years with clear ocular media (patients aged 55–59 had to be in AMD Category 3 or 4—see below) At least 1 eye had to be free from any vision-threatening eye disease other than AMD and cataracts, and that eye could not have had previous ocular surgery except cataract removal. <p><u>Exclusion:</u></p> <ul style="list-style-type: none"> Illness or disorders that would make long-term follow-up or compliance difficult (ie, cancer with a poor 7-year prognosis, major CV or cerebrovascular event within the last year, hemochromatosis) <p><u>Participants were enrolled in 4 AMD categories:</u></p> <ul style="list-style-type: none"> Category 1 (No AMD): free of age-related macular abnormalities; total drusen area less than 5 small drusen (<63 µm); visual acuity ≥20/32 in both eyes. Category 2 (Early AMD): mild age-related macular features (multiple drusen, single or non extensive intermediate drusen [63–124 µm], pigment abnormalities, or any combination of these) in 1 or both eyes, and visual acuity ≥20/32 in both eyes. Category 3 (Intermediate AMD): absence of advanced AMD in both eyes; at least 1 eye with visual acuity ≥20/32 with at least 1 large druse (125 µm), extensive intermediate drusen, or geographic atrophy that did not involve the center of the macula, or any combination of these Category 4 (Advanced AMD): visual acuity ≥20/32 and no advanced AMD (geographic atrophy involving macular center or choroidal neovascularization) in the study eye; the fellow eye had either lesions of advanced AMD or visual acuity <20/32 and AMD abnormalities sufficient to explain reduced visual acuity
Methods	<p><u>Study design:</u></p> <ul style="list-style-type: none"> Multicenter, randomized, double-blind, placebo-controlled trial Patients in Categories 2, 3, and 4 (n=3640) were randomized to 4 treatment groups: (1) antioxidants (500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of β-carotene daily); (2) zinc (80 mg of zinc as zinc oxide and 2 mg of copper as cupric oxide daily); (3) combination of antioxidants and zinc; (4) placebo. Patients in Category 1 (n=1117) were assigned to either antioxidant treatment or placebo. Primary outcome measures were photographic progression to advanced AMD, treatment for advanced AMD, and moderate visual acuity loss. <p><u>Data analysis:</u></p> <ul style="list-style-type: none"> Sample size of 3640 to provide at least 80% power to detect treatment effects Duration of follow-up: minimum of 5 years, average of 6.3 years, maximum of 8 years Intention-to-treat analysis using odds and relative risk ratios Statistical significance: $p \leq 0.01$ at $\alpha = 0.05$ after adjustment for multiple outcomes and interim analyses
Results	<ul style="list-style-type: none"> Patients at high risk for developing advanced AMD (Categories 3 and 4) reduced their risk of developing advanced stages of AMD by about 25% when treated with the combination of antioxidants and zinc (odds ratio = 0.66; 99% CI: 0.47-0.91; $p=0.01$). Patients at high risk for developing advanced AMD who were treated with zinc alone or antioxidants alone reduced their risk of developing advanced AMD by 21%

	<p>(significant) and 17% (not significant), respectively.</p> <ul style="list-style-type: none"> • The combination of antioxidants and zinc statistically significantly reduced the risk of visual acuity loss in Categories 3 and 4 AMD (odds ratio = 0.73; 99% CI: 0.54-0.99; p=0.008) as compared to placebo. Zinc alone and antioxidants alone showed favorable trends on this measure, but the differences were not statistically significant. • No statistically significant evidence of a benefit in delaying progression from Category 2 to Categories 3 and 4 was shown in any treatment group.
Conclusions	<ul style="list-style-type: none"> • Patients at high risk for developing advanced AMD (Categories 3 and 4) should consider taking a supplement of antioxidants plus zinc. • Patients who smoke may want to avoid taking β-carotene. • Data showed some benefit of using zinc alone in reducing the risk of developing advanced AMD. • The effects of using antioxidants alone or substituting other antioxidants, such as lutein, cannot be determined from this trial.
Limitations	<ul style="list-style-type: none"> • 67% of participants also took Centrum. Increases in serum levels of antioxidants and zinc resulting from Centrum intake were negligible compared with increases from the study supplement. • Report of 75% or more compliance in most patients as assessed by pill counts. • Two carotenoids concentrated in the macula, lutein and zeaxanthin, were excluded from the study due to their unavailability. Lutein and zeaxanthin may be beneficial to the macula but whether they can be substituted for β-carotene cannot be answered by the AREDS. • The population in this study was relatively well nourished and may differ from the general population. • Retinal outcomes are based on color 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. • Findings can only be extrapolated to groups 3 and 4 AMD. The occurrence of AMD in groups 1 and 2 was too low to give sufficient power to the findings. • It remains unclear which components of the agent studied were responsible for the changes seen, zinc and antioxidants also showed positive effects used separately. • The non-standardized supply of nutritional supplements will complicate the use of these products for a predictable response. • Long term safety and efficacy of the supplements is unknown. • Use of post-hoc methods to correct for lack of progression to AMD in category 1 and 2 patients. • Use of OR to present outcomes

Data Compilation Tables

Effect of treatment on risk of progression to advanced AMD

	Patients in AMD 2,3,4	Patients in AMD 3, 4
Antioxidants vs. placebo, adjusted	OR: 0.77, NNT 24	OR: 0.76, NNT 18
Zinc vs. placebo, adjusted	OR: 0.71, NNT 20	OR: 0.70, NNT 14
Antioxidants, zinc vs. placebo adjusted	OR: 0.68, NNT 20	OR:0.66, NNT 12
Participants with events	803/3609	775/2556

Acquisition Costs^{9,10}

	Ocuvite PreserVision	ICAPS AREDS Formula	Multivitamin With Minerals	Centrum Silver
Vitamin A	7160 IU	7160 IU	8000 IU	5000 IU
Vitamin C	113 mg	113 mg	120 mg	60 mg
Vitamin E	100 IU	100 IU	30 IU	45 IU
Zinc	17.4 mg (as oxide)	17.4 mg (as oxide)	15 mg	15 mg
Copper	0.4 mg	0.4 mg	2 mg	2 mg
Vitamin B ₂				
Manganese				
Selenium				
Lutein/zeaxanthin				250µg of lutein
Dose	4 tabs/day	4 tabs/day	1 tab/day	1 tab/day
Cost/month	\$10.80	\$17.99	\$0.54	\$2.72

trade_name	va_ppu
VITAMIN C 100MG TAB	\$0.0078
VITAMIN C 250MG TABS	\$0.0073
VITAMIN A 10000UNT CAP	\$0.0130
VITAMIN E 100IU SOFTGEL CAP	\$0.0125
E 100 I.U. CAP VITAMIN E	\$0.0127
VITAMIN E 200 IU SYNTHETIC	\$0.0150
ZINC 50MG TAB	\$0.0119
ZINC 15 TAB	\$0.0139

Conclusions¹¹⁻¹³

The AREDS trial results suggest that antioxidants and zinc, either alone or in combination, were modestly effective for category 3 and 4 patients with AMD. The trials leaves unanswered the question of supplementation for category 1 and 2 patients as well as the long-term safety of the agents. Due to the morbidity of the visual loss associated with AMD and the lack of treatments, it may be reasonable to use supplementation in the selected high-risk group.

References

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