

AXONA[™] FOR ALZHEIMER'S DISEASE: A CLINICIAN'S PERSPECTIVE

Jeffrey L. Cummings, MD

Axona[™] (caprylic triglyceride) is a medical food developed for the clinical dietary management of the metabolic processes associated with mild-to-moderate Alzheimer's disease. Medical foods as a class of intervention alternatives are not well known to most clinicians. Medical foods are defined in the 1988 amendment to the Orphan Drug Act as “a food which is formulated to be consumed or administered enterally (orally) under the supervision of a physician, and which is intended for specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.”¹ Medical foods are distinguished from supplements in that they address a specific identified metabolic condition, and they are typically available only by prescription. They are distinguished from drugs by the absence of a requirement to meet prespecified clinical

outcomes in the management of a specific disease state. Medical foods are regulated by the US Food and Drug Administration (FDA) but are not specifically approved by the FDA in the same way that drug treatments undergo an approval process. The ingredients of medical foods are in the category of generally recognized as safe (GRAS) substances. One medical food is currently marketed in the United States for the management of Alzheimer's disease—Axona. Other medical foods are being developed (eg, Souvenaid[®]), and clinicians can expect to see an increased presence of medical foods in this therapeutic arena.

What Is Axona?

Axona is a formulation of caprylic triglyceride, a medium-chain triglyceride that is metabolized to ketone bodies, predominantly β -hydroxybutyrate (BHB). BHB in turn is metabolized to acetyl-coenzyme A (acetyl-CoA). Acetyl-CoA enters the tricarboxylic acid cycle leading to adenosine triphosphate production. Axona is metabolized to BHB in the liver. BHB serves as an alternate energy substrate for neuronal metabolism. BHB is known to cross the blood-brain barrier and enter the brain. BHB is a common metabolic substrate that is normally produced by the body for neurons in starvation states where glucose is less available.

Dr. Cummings is affiliated with the Departments of Neurology and Psychiatry and Biobehavioral Sciences and the Mary S. Easton Center for Alzheimer's Disease Research at UCLA; David Geffen School of Medicine at UCLA; Los Angeles, California.

Acknowledgments: Dr. Cummings is supported by the Sidell-Kagan Foundation and the Jim Easton Gift.

Disclosure: Dr. Cummings is a consultant for Accera Pharmaceuticals but owns no stock in the company.

Axona in Alzheimer's Disease

The rationale for the use of Axona in Alzheimer's disease is the existence of hypometabolism as a characteristic manifestation of the disease.² Hypometabolism in Alzheimer's disease can be attributed in part to cytotoxic events including tau hyperphosphorylation,² oxidative brain injury, inflammation, and excitotoxicity. Hypometabolism precedes the occurrence of cognitive impairment and can be demonstrated in at-risk individuals prior to the onset of cognitive compromise.³ Evidence from insulin infusion studies shows that neurons in Alzheimer's disease patients are utilizing glucose suboptimally and cognition can be enhanced in the course of insulin infusion experiments.⁴ In these studies, efficacy was noted in subjects who did not carry the primary genetic risk factor for Alzheimer's disease—the epsilon 4 variant of the apolipoprotein E gene (*APOE* ε4). Long-term treatment with insulin is therapeutically implausible, and providing neurons with an alternate energy substrate to optimize neuronal metabolism provides the theoretical framework for the use of ketone bodies in Alzheimer's disease.⁵

Clinical Trials of Axona in Alzheimer's Disease

Medical foods are not required to meet the same evidentiary standards as drugs. Anti-Alzheimer's disease therapies must demonstrate a significant drug-placebo difference on a valid measure of cognition and on a measure of clinical meaningfulness (global scale or activities of daily living scale) in two well-conducted clinical trials. These standards do not apply to medical foods. Medical foods are required to address a recognized metabolic condition in a disease

state, must be taken orally, and must not be part of an individual's normal diet.^{1,6} Supplements are distinguished from medical foods in being part of one's normal diet, although often taken in higher than usual amounts.

Reger et al⁷ performed a double-blind crossover of a single dose of medium-chain triglyceride (given as 40 or 80 g rather than the 20 g currently recommended in the Axona package insert⁸) to patients with Alzheimer's disease or mild cognitive impairment. Patients were prescreened for *APOE* ε4 carriage status. Similar to earlier work with glucose and insulin, patients who were *APOE* ε4 non-carriers showed a significant improvement on the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog) when Axona was administered. There was no effect of Axona in the ε4 carrier patients. The report does not specify whether response by ε4 carrier status was anticipated and prespecified. Significant increases in BHB levels were measurable in plasma 90 minutes after treatment. Significant correlations were observed between paragraph recall and BHB levels.

A second study describing Axona management of patients with Alzheimer's disease is summarized in the package insert.⁸ This was a 90-day, randomized, double-blind, placebo-controlled, parallel group clinical trial including 152 patients with mild-to-moderate Alzheimer's disease. Eighty percent of the patients were taking Alzheimer's disease therapy. Patients received 10 g/day of Axona on days 1 through 7 and then 20 g/day of Axona on days 8 through 90. There was a significant product-placebo difference

in favor of Axona at day 45 (1.91 ADAS-cog; $P = .024$) and a trend towards improvement in the Axona group, compared with placebo at day 90 (ADAS-cog difference 1.54; $P = .0767$). When the sample was analyzed according to $\epsilon 4$ carrier status, there was a significant product-placebo difference favoring Axona at both day 45 and 90 in the non-carrier group, whereas the $\epsilon 4$ carriers showed no benefit from Axona. Gastrointestinal disturbances were the most common recorded adverse events in the clinical trials. In the 90-day study, 24.4% of patients taking Axona experienced diarrhea compared with 13.6% in the placebo group. Flatulence was noted in 17.4% of Axona-managed patients compared with 7.6% of those receiving placebo; dyspepsia was present in 9.3% of Axona-managed patients and 4.5% of those receiving placebo. Gastrointestinal side effects are reportedly reduced by administration of Axona with a meal or mixing it with a drink.

The available formulation of Axona comes as a powder and is mixed with 4 to 8 oz of water. It is shaken until blended and consumed immediately after preparation. Axona contains caseinate (milk-derived protein), whey (milk), and lecithin (soy) and should not be used in patients allergic to these ingredients.⁸ Axona induces a ketotic state and should be used with caution in patients at risk for ketoacidosis (eg, alcoholics or poorly controlled diabetics).⁸ Elevated triglycerides can also occur and should be monitored periodically in individuals with risk factors for the metabolic syndrome (elevated waist circumference [≥ 40 inches in men, ≥ 35 inches in women], blood pressure $\geq 130/85$ mm Hg, reduced fasting HDL cholesterol levels [< 40 mg/dL in men, < 50

mg/dL in women], or fasting glucose levels ≥ 100 mg/dL).⁸ No ill effects of long-term ketosis have been observed in children treated with ketotic diets for epilepsy; the effects of long-term ketosis in the elderly are unknown. The pharmacokinetics of Axona, such as half-life, are not reported. The impact of Axona on commonly used biomarkers of Alzheimer's disease, such as fluorodeoxyglucose positron emission tomography (FDG-PET), have not yet been systematically studied.

Integrating Axona Into the Care of Patients With Alzheimer's Disease

Comprehensive care of patients with Alzheimer's disease includes pharmacotherapy, recommendations for optimal control of comorbid medical illnesses (especially hypertension and

“Medical foods represent a new alternative to be considered for integration into a comprehensive therapeutic regimen for patients with Alzheimer's disease.”

hypercholesterolemia), diet, exercise, and social interaction. Epidemiologic evidence linking deferred onset of Alzheimer's disease to diets high in antioxidant content has prompted many patients to take and many physicians to recommend antioxidants for Alzheimer's disease. Medical foods represent a new alternative to be considered for integration into a comprehensive therapeutic regimen for patients with Alzheimer's disease. Substantial data exist for the presence of hypometabolism as one manifestation of Alzheimer's disease.^{2,5,9} Evidence

from masked randomized trials suggests benefit from Axona in patients with Alzheimer's disease.⁷ The effect, however, was evident only in $\epsilon 4$ non-carriers. Details of the randomized 90-day Axona trial are available only in preliminary form in the package insert. Axona is not without side effects: patients and caregivers must be alerted to the possible occurrence of diarrhea, and patients at risk for the metabolic syndrome or ketoacidosis must be carefully monitored.

A New Element for the Comprehensive Management of Patients With Alzheimer's Disease

Use of Axona should be discussed with patients and caregivers in terms of the available data on efficacy and side effects. The clinical data to date suggest that Axona may provide benefit only in *APOE* $\epsilon 4$ non-carriers. Clinicians, patients, and caregivers must decide whether genotyping is indicated. If gene testing is pursued, genetic counseling should be available for the interpretation of genotype information. Genotyping has implications for future generations, and the information requires thorough

discussion to ensure that the patient and family fully understand its implications. Patients and caregivers are eager to try new interventions that may ameliorate the symptoms or progression of Alzheimer's disease. Axona represents a new element in this dialogue. It can be recommended for selected patients after discussion of the evidence for benefit and harm.

References

1. US Food and Drug Administration. Section 5 Orphan Drug Act. 1988. Available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/ucm109555.htm>. Accessed June 17, 2009.
2. Costantini LC, Barr IJ, Vogel JL, Henderson ST. Hypometabolism as a therapeutic target in Alzheimer's disease. *BMC Neuroscience*. 2008;9 (Suppl 2):S16.
3. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med*. 1996;334(12):752-758.
4. Craft S, Newcomer J, Kanne S, et al. Memory improvement following induced hyperinsulinemia in Alzheimer's disease. *Neurobiol Aging*. 1996;17(1):123-130.
5. Henderson ST. Ketone bodies as a therapeutic for Alzheimer's disease. *Neurotherapeutics*. 2008;5(3):470-480.
6. US Food and Drug Administration. Guidance for Industry: Frequently Asked Questions About Medical Foods. 2007. Available at: <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/MedicalFoods/ucm054048.htm>. Accessed June 18, 2009.
7. Reger MA, Henderson ST, Hale C, et al. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol Aging*. 2004;25(3):311-314.
8. Axona [package insert]. Broomfield, CO: Accera, Inc.; 2008.
9. Mosconi L, Brys M, Glodzik-Sobanska L, et al. Early detection of Alzheimer's disease using neuroimaging. *Exp Gerontol*. 2007;42(1-2):129-138.

Copyright © Quadrant HealthCom Inc. 2009. All rights reserved. NLR0903. This publication may contain information on products, uses, and dosage forms recently approved, or not yet approved, by the U.S. Food and Drug Administration. This report is prepared independent of any medical association or organization. Promotional claims are unintended; such mention is for educational purposes only. This report was made possible through an unrestricted grant from Accera, Inc. AC-09-090