Axona® Medical Food
Information for Health Care Professionals

DESCRIPTION

Axona® is a medical food‡ containing a proprietary formulation of medium-chain triglycerides (MCTs), specifically caprylic triglyceride, for the clinical dietary management of mild to moderate Alzheimer's disease (AD). Axona® addresses a distinctive nutritional requirement associated with impaired cerebral glucose metabolism in AD patients by providing specially modified nutritional support to ensure delivery of MCTs to the small intestine to safely elevate serum ketone levels without inducing ketoacidosis. Axona® thereby provides brain cells with an alternative energy source to glucose, essential for proper neuronal function. This nutrient need in AD cannot be met by modification of the normal diet alone.

Axona® is intended for oral administration once a day and must be used under the supervision of a physician.

METABOLIC IMPAIRMENT IN ALZHEIMER'S DISEASE

Under normal conditions, glucose is the primary energy source for the brain. Imaging studies have shown decreased utilization of glucose in the brains of AD patients early in the disease, before clinical signs of cognitive impairment occur. This decrease in cerebral glucose metabolism (hypometabolism) worsens as clinical symptoms develop and the disease progresses.[1,2] Hypometabolism may not be solely an artifact of cell atrophy since it occurs in asymptomatic patients at risk for AD, such as patients homozygous for the epsilon 4 variant of the apolipoprotein E gene (APOE4), a genetic risk factor for AD), as well as in familial forms of AD. Thus, while AD is a complex disease, the etiology of which is multifactorial, scientific research demonstrates there are distinctive metabolic impairments and nutritional requirements characteristic of AD.[3,4]

Given that hypometabolism is an early and progressive event in AD and may precipitate downstream pathological events, it is reasonable to target the improvement of neuronal energy states for the management of AD. Studies in animals and human subjects have shown that increasing blood glucose levels facilitates memory.[5] However, due to the impracticality of maintaining chronically elevated glucose levels, a safer alternative is required. Ketone bodies provide an alternative energy substrate that can be utilized by the brain to improve cognition and memory.

Ketone bodies are naturally produced from fat stores as an alternative to glucose during periods of sustained hypoglycemia, such as during fasting or very low carbohydrate intake. In a controlled clinical study in human subjects experiencing hypoglycemia, the infusion of ketones was shown to improve cognitive function compared with control subjects, suggesting that increased ketones can substitute for glucose as an energy source for the brain.[6,7]

In vitro data indicate that the ketone body ß-hydroxybutyrate (BHB) can substitute for a large fraction of glucose as an energy substrate, and preserves neuronal integrity and stability.[8] Ketone bodies feed directly into the tricarboxylic acid (TCA) cycle in neurons and generate adenosine triphosphate (ATP), as well as increasing pools of acetyl-CoA and succinate. Ketones are neuroprotective against several types of toxic insults,[9] and also reduce neuropathological changes, such as ß-amyloid levels in animal models of AD.[10]

MECHANISM OF ACTION/METABOLISM

Axona® provides a simple and safe method to induce ketosis, thus providing an alternative energy substrate to glucose in the brain of patients with AD. After oral administration, Axona® is processed by lipases in the gut, and the resulting medium-chain fatty acids (MCFAs) are absorbed into the portal vein. The MCFAs rapidly pass directly to the liver, where they undergo obligate oxidation.[11] MCFAs enter the liver mitochondria as acyl-CoA, where they undergo ß-oxidation to form acetyl-CoA and acetoacetyl-CoA, which, when produced in excess, are combined to form 3-hydroxy-3-methyl-glutaryl- CoA (HMG-CoA). HMG-CoA is then acted on by HMG-CoA lyase to form acetoacetate and BHB, i.e., ketone bodies. Since the liver does not use ketone bodies, they are released into the circulation to be used by extrahepatic tissues.

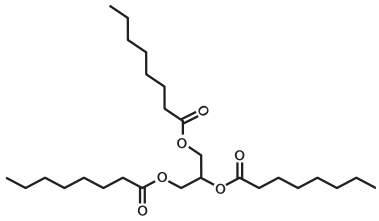
The ketone body BHB crosses the blood-brain barrier and is then taken up by neurons. Ketones are used in a concentration-dependent manner in the adult human brain, including the elderly brain[12,13] until circulating concentrations reach approximately 12 mM, at which point they saturate the oxidative machinery.[14] In neurons, ketone bodies enter the mitochondria to produce a cascade effect on mitochondrial activity that increases mitochondrial efficiency and thereby reduces the generation of reactive oxygen species. Ketone bodies feed directly into the TCA cycle in neurons and generate ATP, as well as increase pools of acetyl-CoA and acetylcholine. Ketone bodies are used by neurons even in the presence of abundant glucose.

INGREDIENTS

Axona® is a proprietary formulation of >95% pure caprylic triglyceride. Axona® also contains acacia, a soluble dietary fiber which serves to encapsulate the caprylic triglyceride to allow for small drops of oil to be released into the small intestine and enhance digestion and absorption of caprylic triglyceride.

Structure of Caprylic Triglyceride

Caprylic triglyceride is a medium-chain triglyceride (MCT) that is Generally Recognized As Safe (GRAS) for its intended use as medical food, self-affirmed†). For a substance to be GRAS, the Food and Drug Administration (FDA) requires that the substance be generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures to be safe under the conditions of its intended use.



1,2,3-Tricapryloyl-sn-glycerol
Molecular weight = 470.70

Ingredient List in Descending Order of Quantity by Weight

Caprylic Triglyceride, Acacia, Contains 2% or less of Silicon Dioxide.

Produced in a facility that may process milk, eggs, fish, crustaceans, nuts, peanuts, wheat, soy, and sulphites.

ADMINISTRATION

Axona® is taken orally once a day, 30 minutes after finishing a full meal (preferably breakfast or lunch, whichever is more substantial). Patients should start with a graduated portion regimen for 7 days, or as directed by the supervising healthcare provider, before taking one full packet (40 grams) per day. Axona® should be added to 4 to 8 ounces (118 to 236 milliliters) of water or other liquids as preferred, and shaken or blended until fully mixed.

MEDICAL SUPERVISION & INSTRUCTIONS FOR USE

Axona® is a medical food product and must be used under medical supervision. Both patients and caregivers should be instructed in the correct administration amount and schedule for Axona® based on medical evaluation of the patient by the supervising healthcare provider. Patients and their caregivers should be counseled that mild GI symptoms (diarrhea, flatulence, dyspepsia, and feeling of "unsettled stomach") may be experienced by some individuals who take Axona®. Taking Axona® 30 minutes after finishing breakfast or lunch may alleviate GI symptoms.

Starting Axona®

It is recommended that patients start Axona® using a graduated portion regimen. During the first week of product administration, patients should start with 1 tablespoon (~8-10 g) daily for 2 days, and increase the serving size by 1 tablespoon (~8-10 g) every other day as tolerated until the full dose (~5 tablespoons/40g) is taken. A small minority of patients may require a more gradual titration.

Axona® should always be taken 30 minutes following completion of a full meal.

Axona® Graduated Portion Plan

	Grams	Portion Using 40 g Packet
Day 1	10	1 tablespoon
Day 2	10	1 tablespoon
Day 3	20	2 tablespoons
Day 4	20	2 tablespoons
Day 5	30	3 tablespoons
Day 6	30	3 tablespoons
Day 7 (and beyond)	40	Full 40 g packet and take as directed

Taking Axona®

The therapeutic serving amount of Axona® (one packet/40g) should be taken once a day 30 minutes following completion of a full meal (preferably breakfast or lunch, whichever is more substantial).

PACKAGING

Axona® is supplied as a powder in individual packets of 40 grams (containing 20 grams caprylic triglyceride). Commercial product is supplied in a carton containing 15 packets.

Product	Product Code	Usage
Commercial Product [15 40-gram packet]	42907-040-30	Physician Supervision

CLINICAL STUDIES

Cerecin's caprylic triglyceride products have been tested in several clinical trials in populations of patients with a diagnosis of probable mild to moderate AD and MCI, as well as in normal elderly volunteers. Results of these studies are available in the referenced publications, on clinicaltrials.gov, and about-axona.com and from Cerecin upon request.

Single-Administration Clinical Study in Patients with AD or MCI[15]

The first clinical study was a randomized, placebo-controlled, crossover-design study to measure the therapeutic effects of a single administration (40-80 grams) of caprylic triglyceride on memory in 20 patients between the ages of 55-85 years and diagnosed with probable AD (n = 15) or MCI (n = 5). The mean baseline score in the Mini-Mental State Examination (MMSE; a test used in the diagnosis of AD) was 22.2. Subjects were allowed to continue on stable concomitant AD treatments. A single 40-gram administration of caprylic-triglyceride led to elevated BHB serum levels (to approximately 0.5 mM at 90 minutes following administration) that were positively correlated with improvement in paragraph recall (a measure of cognition) (P = 0.02). APOE4(–) patients showed greater improvement compared with APOE4(+) patients in the AD Assessment Scale—Cognitive subscale (ADAS-Cog, which measures memory and other aspects of cognitive performance) (P = 0.039).

Clinical Study in Patients with Probable Mild to Moderate AD[16]

The second clinical study was a DB, randomized, placebo-controlled, 90-day study with a 2-week washout period performed at multiple US clinical centers in a population of 152 patients with mild to moderate AD, randomized 1:1 to receive placebo or Axona. At day 45, ADAS-Cog scores stabilized in the Axona group, whereas a decline in cognition was observed in the placebo group. The point difference in ADAS-Cog change from baseline scores at day 45 between groups was 1.91 (P = 0.024; see Figure 1). The point difference in ADAS-Cog change from baseline scores at day 90 between groups was 1.54 (P = 0.0767). Final ADAS-Cog evaluations were performed following a 2-week washout period (day 104): the Axona group maintained a slight improvement from baseline, whereas the placebo group still demonstrated a decline, although the difference between groups was no longer statistically significant (P = 0.405).

As defined in the Study Statistical Plan, the ADAS-Cog change from baseline score was also analyzed in subgroups of patients based on APOE4 genotype. The APOE4(–) patients receiving Axona showed improved cognitive function when compared with APOE4(–) patients receiving placebo (n = 29, Axona; n = 26, placebo). The point difference in change from baseline ADAS-Cog scores for APOE4(–) Axona and placebo patients at day 45 was 4.77 (P < 0.0005), and was 3.36 at day 90 (P = 0.015; see Figure 2). In APOE4(+) patients (n = 38, Axona; n = 31, placebo), the mean change in ADAS-Cog total scores for the 2 groups was essentially identical at all time points, with more patients showing decline rather than improvement at day 45 and day 90. Additional analyses were performed among patients who were dosage compliant (defined as patients who reported consuming at least 80% of the total intended dose). In this subset, the difference from baseline in ADAS-Cog scores between Axona and placebo groups was more pronounced than that observed in the overall study population. Among dosage-compliant patients, the difference in change from baseline ADAS-Cog scores between Axona and placebo groups at day 45 was 2.60 points (P = 0.0215) and at day 90 was 2.26 points (P = 0.064) (Figure 1). Among E4(–) dosage-compliant subjects, a significant difference in change from baseline in ADAS-Cog scores between Axona and placebo groups was notable on day 45 (6.26-point difference; P = 0.001) and day 90 (5.33-point difference; P = 0.006) (Figure 2). Among E4(+) dosage-compliant subjects, there was no significant difference in change from baseline in ADAS-Cog scores between those administered Axona and placebo.

Figure 1: Improvements in ADAS-Cog for all patients with Alzheimer's disease.

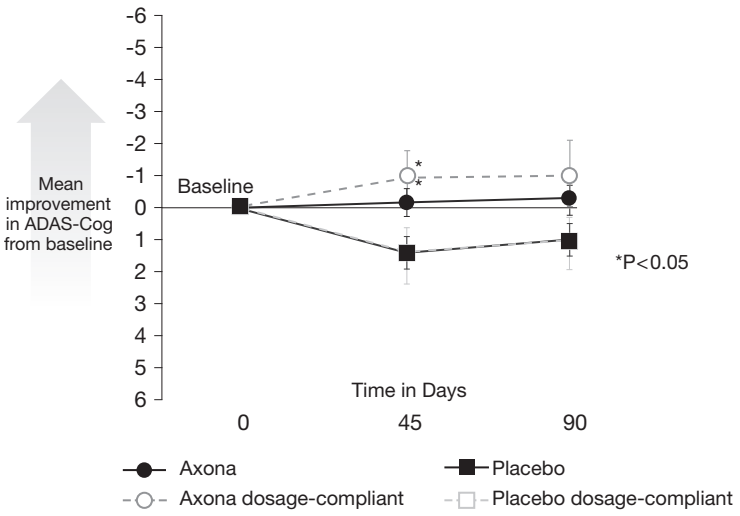
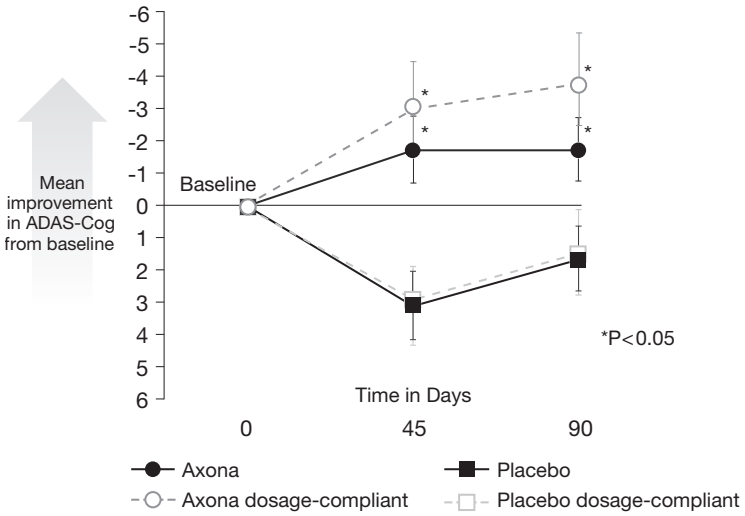


Figure 2: Significant improvements in ADAS-Cog for APOE4 (-) patients.



An additional double-blinded, placebo-controlled, randomized clinical trial was conducted in sixteen subjects with mild-to-moderate AD, based on NINCDS-ADRDA criteria. Subjects received four ^{15}O-water PET scans over the course of the study to assess regional cerebral blood flow (rCBF): once before receiving a 40 g dose of Axona or placebo and 90 minutes after the dose, on the first day, and again after 45 days of daily Axona or placebo consumption. The scans were examined by standardized volumes of interest (sVOI) and voxel-based statistical parametric mapping (spm) methods of analysis. Results showed that in subjects lacking an APOE4 allele rCBF in the left superior lateral temporal cortex was significantly elevated by sVOI analysis after adopting an Axona diet for 45 days (p=0.04). This was further corroborated by spm. The anterior cerebellum, left inferior temporal cortex, and hypothalamus were also found by spm to be regions of long-term increase in rCBF in these subjects.[17]

POTENTIAL ADVERSE REACTIONS

Clinical Study Experience: Based on the 9 caprylic triglyceride studies conducted to date that included safety investigations, caprylic triglyceride formulations are safe and well tolerated by both healthy subjects and those with mild to moderate AD.

Thus far, a total 740 subjects have been enrolled in nine clinical studies sponsored by Cerecin testing caprylic triglyceride. Because clinical studies are conducted under varying conditions, AE rates cannot be directly compared to rates in clinical studies of other compounds, and may not reflect the rates observed in practice.

As observed in studies KET-02-001 (AD subjects), KET-04-001 (AD subjects), and KET-08-004 (healthy subjects), caprylic triglyceride was safe and well tolerated.

As observed in studies AC-12-010 (AD subjects), AC-16-011_BE (healthy subjects), AC-16-012_BE (healthy subjects) and AC-16-013_BE (healthy subjects), caprylic triglyceride was well tolerated (mixed in either water or Ensure®) with AEs being primarily limited to GI disorders consisting of mild to moderate nausea, vomiting, abdominal discomfort, abdominal distension and dyspepsia. Discontinuations were predominantly due to AEs of the GI system and included diarrhea, nausea, abdominal distension, abdominal discomfort, upper abdominal pain and dyspepsia.

As observed in studies AC-17-014_BE (healthy subjects) and AC-18-016_FE (healthy subjects), single oral dose of caprylic triglyceride is safe and well tolerated with a standard breakfast (and caprylic triglyceride oil with both a standard and high-fat breakfast). Medium-chain triglycerides are considered saturated fats, as are many long-chain triglycerides (LCTs). However, MCTs are metabolized differently from LCTs in that they do not significantly increase cholesterol levels and are not stored as fat. In a 14-day, open-label bridging study with Axona, no clinically significant changes in cholesterol, low-density lipoproteins (LDL), or high-density lipoproteins (HDL) were observed. In a 16-week, randomized, controlled study in 31 patients receiving a reduced-calorie diet containing either olive oil or MCT oil (18-24 grams daily), significant and comparable reductions in total cholesterol and LDL were observed in both study groups.[18]

Voluntarily Reported Post-Market AEs: Consistent with AEs reported during clinical trials, spontaneously reported AEs consisted primarily of abdominal discomfort, diarrhea, nausea, and dyspepsia. Fainting and dizziness were also reported in <1 in 500 patients taking Axona. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to exposure to the product.

NUTRIENT - DRUG INTERACTIONS

Subjects enrolled in AD trials who were receiving commonly prescribed medications for AD were allowed to remain on these medications as long as they had been receiving stable doses for at least 3 months and remained on stable doses throughout the course of the study. No safety issues occurred to suggest that the nutrients in Axona® interact with AD medications. Axona® may be administered along with prescribed AD medications.

USE IN SPECIFIC POPULATIONS

Axona® has been tested in clinical studies of normal elderly subjects, and patients with mild cognitive impairment (MCI) or mild to moderate AD between the ages of 50 and 93 years. To date, there have been no clinical studies of Axona® performed in other specific patient populations (pregnant or lactating women, pediatric, hepatic insufficiency, renal insufficiency, or immunological insufficiency). Axona has not been studied in patients with severe AD. No significant findings were associated with patient responses by sex, race, or ethnicity.

NONCLINICAL TOXICOLOGY

Medium-chain triglycerides exhibit very low levels of toxicity in humans and several species of animals when administered orally or by other routes. The prescribed daily exposure of Axona will be 0.29 grams/kg/day in a 70-kg patient. This exposure is ~33 times lower than the "No Observed Adverse Effect Level" (NOAEL) (10 milliliters/kg or ~9.5 grams/kg) of MCTs in rats following 30 days or 182 days of oral administration, and ~8 times lower than the NOAEL (2.5 milliliters/kg or ~2.37 grams/kg) in a 2-year study in rats. The acute oral lethal dose, 50%, for MCTs is >24 grams/kg in mice, and >34 grams/kg in rats. Daily administration of 2.9 grams MCTs (11-20 grams/kg/day range) for 30 days in rats did not demonstrate toxicity. In ocular and dermal irritation testing, MCTs exhibited little potential for irritation, even with prolonged eye or skin exposure. MCTs did not induce hypersensitivity or photosensitivity, and extensive animal toxicity studies indicated that MCTs are not reproductive or developmental toxicants.

MCTs have not shown significant genotoxicity in bacterial mutagenicity, chromosome aberration, sister chromatid exchange, micronucleus, or host-mediated mutagenicity assays, and are negative for carcinogenicity in rats. An increased incidence of pancreatic and fore stomach hyperplasia and adenoma was noted at 5 and 10 milliliters/kg, with increased mortality at 10 milliliters/kg, but no carcinomas were observed. In vitro data suggest that MCTs are immunomodulatory; however, this in vivo oral study measuring immune system endpoints was confounded by the presence (in the treatment diet) of long-chain fatty acids, which have been shown to induce effects on spleen lymphocytes. In clinical studies utilizing Axona, no statistically significant or clinically meaningful changes from screening to end of study were seen between groups for mean values of immune parameters. Therefore, the immunomodulatory effects of MCTs following oral administration are minimal.

CONTRAINDICATIONS

Axona® should not be taken by patients allergic to any of its component ingredients or their sources.

WARNINGS AND PRECAUTIONS

Axona® should be used with caution in patients at risk for ketoacidosis, for example, patients with a history of alcohol abuse and poorly controlled diabetics.

In general, adverse events associated with MCTs include gastrointestinal symptoms (e.g., abdominal cramping, diarrhea, and dyspepsia). This may be due to rapid hydrolysis of MCTs in the gut and the resultant accumulation of high concentration of medium-chain fatty acids in the small intestine.[19] For this reason, Axona® should be used with caution in patients with a history of GI inflammatory conditions, such as irritable bowel syndrome, diverticular disease, chronic gastritis, and severe gastroesophageal reflux disease (see "Medical Supervision & Instructions for use").

The dose-limiting toxicity with MCTs is known to be diarrhea. Animal studies have shown that consuming the equivalent of up to 33 times the recommended human administration of Axona® for 3 months had no adverse effects.[20] In the event of overusage of Axona®, patients should be managed with systematic and supportive care as soon as possible. Overusage symptoms could vary by patient. Severe episodic diarrhea may occur.

Fainting and dizziness have been infrequently reported (in <1 in 500 patients using Axona®), principally among patients with a history of bradycardia or hypotension, or among patients taking medications that may induce these effects (e.g., antihypertensives and cholinesterase inhibitors).

The importance of taking Axona® following a meal should be emphasized especially for patients who may be at risk for development of these symptoms.

Mild increases in blood urea nitrogen (BUN), creatinine, or uric acid were occasionally observed among patients receiving Axona® in one clinical trial. In all but two cases, these laboratory increases did not exceed 1.5 times upper limit of normal (ULN). Although none of the clinical investigators assessed these laboratory abnormalities as being clinically significant or as being associated with the development of adverse events (AEs), a possible relationship to Axona® cannot be entirely ruled out.

Healthcare providers should discuss the importance of routine renal function test monitoring with their patients who have a history of renal dysfunction.

Elevated triglyceride values were observed in some subjects who presented with probable metabolic syndrome. Triglyceride (TG) levels should be periodically monitored in patients who meet at least 3 of the following 5 criteria indicative of metabolic syndrome: elevated waist circumference (≥40 inches in men, ≥35 inches in women), BP ≥130/85 mm Hg, TG ≥150 mg/dL, reduced fasting HDL (<40 mg/dL in men, <50 mg/dL in women), and fasting glucose ≥100 mg/dL.

A small minority of patients appear to be more likely to experience GI adverse events to the amount of MCTs contained in Axona®. Susceptible patients may include those with a history of GI disorders, fainting or dizziness, presence of bradycardia and/ or hypotension, and patients who are taking other medications that have known side effects of fainting/dizziness. If adverse events occur, discontinue Axona® until symptoms resolve (generally within 2-3 days). Restart Axona® beginning with the 1-tablespoon serving size.

In addition, the following recommendations may help improve tolerability: Taking Axona® following a meal containing fats and proteins may slow the digestion of the MCTs contained in Axona® and reduce the likelihood of developing GI symptoms. Adding ice to the drink may also slow digestion and reduce potential side effects. In addition, tolerability can be improved if patients sip the drink over a period of 30 minutes instead of drinking it all at once.

Patients should seek the advice of their healthcare provider if any GI or other adverse events persist.

STORAGE

Axona® should be stored at room temperature, 15°C-30°C (59°F-86°F), sealed, and protected from light and moisture. Reconstituted product may be refrigerated and stored for up to 24 hours. Refrigerated product should be re-blended and thoroughly mixed prior to consumption.

‡ The statutory definition of "medical food" is found in section 5(b) of the Orphan Drug Act at: 21 U.S.C. § 360ee(b) (3). A medical food is a specially formulated food, intended to be consumed or administered enterally under the supervision of a physician, for the dietary management of a disease or condition for which distinctive nutritional requirements exist, based on reliable scientific evidence. FDA's regulation establishing criteria for a medical food to be exempt from the agency's nutrition labeling requirements are found at 21 C.F.R. § 101.9 (j)(8).

† GRAS Report, entitled "Captrin: GRAS (Generally Recognized As Safe) in Alzheimer's Disease Patients Report," authored by a panel of experts in the field, a Confidential Report on file at Cerecin, Inc.

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For more information, visit www.about-axona.com.
Patents issued: USP 6,835,750, USP 8,426,468,
EP 1292294 and patents pending
AC-19-853

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