Accera®

November 2012

AXONA® DESCRIPTION

1. Indications and Usage

Axona (caprylidene) is a medical food (see Section 11 "Description" below) containing a proprietary formulation of medium-chain triglycerides (MCTs), specifically caprylic triglyceride, for the clinical dietary management of the metabolic processes associated with mild to moderate Alzheimer's disease (AD). Axona is taken orally once a day and must be administered under medical supervision.

Alzheimer's Disease as a Metabolic Deficiency

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 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, AD is a disease with distinctive metabolic and nutritional requirements.[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 β-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 β-amyloid levels in animal models of AD.[10]

Axona is designed to safely elevate serum ketone levels to assist with the clinical dietary management of the metabolic processes and nutritional requirements associated with mild to moderate AD.

2. Administration

Axona is taken orally once a day shortly after a full meal (preferably breakfast or lunch, whichever is more substantial). Patients should start with a graduated dosing regimen for 7 days, or as directed by the supervising healthcare provider, before taking one full packet (40 grams) per day (see Section 17 "Patient Counseling Information" for graduated dosing instructions). 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. A small minority of patients may require a more gradual dose titration.

3. Forms and Strengths

Axona is available in individual packets of 40 grams of powder containing 20 grams caprylic triglycerides. Commercial product is supplied in a carton containing 30 packets. Professional sample product is available in a Graduated Dosing Plan carton containing 16 10-gram packets.

Product	Product Code	Usage
Commercial Product [30 40-gram packets]	**42907-040-30**	Rx only
Sample Product [16 10-gram packets]	**42907-040-16**	Professional Samples—Not for sale

4. Contraindications

Axona should not be taken by patients allergic to milk or soy.

5. Warnings and Precautions

Axona contains caseinate (milk-derived protein), whey (milk), and lecithin (soy). Do not use in patients allergic to these component ingredients, or their sources, that is, milk or soy.

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 (eg, 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.[11] 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 Section 17 "Patient Counseling Information").

Fainting and dizziness have been infrequently reported (in <1 in 500 patients filling prescriptions for Axona), principally among patients with a history of bradycardia or hypotension, or among patients taking medications that may induce these effects (eg, 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. In addition, the gradual dose titration plan should be used for this at-risk population (see Section 17 "Patient Counseling Information").

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 x 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.

6. Adverse Reactions

Clinical Study Experience

Thus far, a total of 197 subjects have received Axona in one of 3 clinical trials. 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.

Single-Administration Study: The first clinical trial was a randomized, placebo-controlled, crossover-design study to measure the potential therapeutic effects on memory of a single administration of Axona (40-80 grams of MCTs) in 20 patients between the ages of 55-85 years old and diagnosed with probable AD (n = 15) or mild cognitive impairment (MCI) (n = 5).[12] Two subjects experienced AEs primarily associated with the GI system, including nausea, abdominal discomfort, and diarrhea.

Alzheimer's Disease Study: The second clinical study was a double-blind (DB), randomized, 90-day, placebo-controlled study performed at multiple US clinical centers in a population of 152 patients with mild to moderate AD.[13] In addition, subjects completing the 90-day trial were permitted to enroll in an optional 6-month, open-label (OL) extension study. Patients received 10 grams of caprylic triglyceride per day on days 1-7 and 20 grams of caprylic triglyceride per day on days 8-90. Seventy-six percent of Axona subjects (compared with 62% of placebo subjects) experienced at least one AE during the course of the study, the majority of which were mild to moderate in severity. The most frequently reported AEs involved the GI system, in which 48.8% of Axona and 27.3% of placebo subjects experienced one or more AEs. The primary GI AEs occurring more frequently in the Axona than in the placebo group consisted of: diarrhea (24.4% vs 13.6%), flatulence (17.4% vs 7.6%), and dyspepsia (9.3% vs 4.5%). AEs reported among the 49 subjects in the OL phase of the study were consistent with those observed in the DB phase.

The following table presents the number and percentage of AD patients in the DB AD study who developed the most commonly reported AEs (occurring more frequently in Axona than in placebo subjects and in at least 3% of patients receiving Axona).

Adverse Events Reported in ≥3% of Axona Patients*

	AD Study Placebo (n = 66)		AD Study Axona (n = 86)	
	n	%	n	%
Any Event	41	62.1	65	75.6
Diarrhea	9	13.6	21	24.4
Flatulence	5	7.6	15	17.4
Dyspepsia	3	4.5	8	9.3
Dizziness	4	6.1	6	7.0
Headache	1	1.5	5	5.8
Abdominal pain	3	4.5	4	4.7
Urinary tract infection	3	4.5	4	4.7
Hypertension	2	3.0	4	4.7
Pain	2	3.0	3	3.5
Rhinitis	2	3.0	3	3.5
Fatigue	1	1.5	3	3.5
Coughing	0	0	3	3.5

*Reported more frequently in Axona than in placebo patients.

Bridging Study: The third clinical study was a 14-day, open-label, randomized trial performed at 4 US clinical centers in 66 normal elderly volunteers. Three formulations of Axona were administered for 14 days either with a 7-day titration (7 days at 10 grams caprylic triglyceride followed by 7 days at 20 grams caprylic triglyceride) or without titration (14 days at 20 grams caprylic triglyceride). The original formulation utilized in the DB AD study was compared with 2 formulations that contained different ratios of proteins to carbohydrates. Subjects within each cohort experienced comparable frequencies of AEs, including those within the GI system. The most common AEs, consisting of nausea (19.7%), abdominal distension (16.7%), flatulence (15.2%), and diarrhea (13.6%), were generally transient in nature and resolved without treatment. In addition, 7 subjects developed clinically significant increases in triglyceride values after Axona administration. Six of these 7 subjects were identified as having probable metabolic syndrome. Of note, dietary restrictions were not imposed during this study, and neither the quantity nor the quality of food consumption was monitored. Therefore, although a causal relationship to Axona was not determined, triglyceride levels should be periodically monitored in patients receiving Axona who meet criteria indicative of metabolic syndrome.

Gastrointestinal: In each of the 3 clinical studies, AEs occurring within the GI system were the most commonly experienced events, and in general, the most frequently reported AEs consisted of diarrhea, flatulence, and dyspepsia. Mild "queasiness" or nausea that was transient in nature was also occasionally reported, as were "bloating" and abdominal discomfort. In the DB AD study, the overall rate of severe GI events in Axona patients included diarrhea (5.8%), dyspepsia (2.3%), and flatulence (1.2%). In all but 2 cases, the diarrhea spontaneously resolved without treatment. The majority of GI events were mild to moderate in severity, and it was found that the severity of AEs could be reduced if Axona was taken with food. In the DB AD study, the incidence of severe diarrhea declined from 9.7% to 3.1% following a change in mixing instructions (blending the original formulation of Axona with a meal replacement drink such as Ensure® instead of water). The marketed formulation of Axona does not require mixing with Ensure (see Section 14 "Clinical Studies" and Section 16 "How Supplied/Storage and Handling" below).

Renal Function: In the DB AD clinical study, mean values in BUN, uric acid, and creatinine increased from screening values in the Axona group; however, in 5 of 7 cases these laboratory increases did not exceed 1.5 x ULN. One subject with a recent history of renal failure requiring dialysis had an elevated BUN value that was 2.4 x ULN. Another patient who had been receiving long-term therapy with medications associated with elevated renal function test results (ie, an angiotension II receptor antagonist and furosemide) developed increased BUN and creatinine values up to 2.5 x ULN. The majority of subjects with significant renal function test abnormalities were also noted to have abnormal values at screening, were taking concomitant medications associated with elevated renal function test results, and had BUN/creatinine ratios >15, indicative of dehydration. While the increases in these renal function tests appear to be related to either pre-existing conditions or to dehydration, a relation to Axona cannot be entirely ruled out.

Other Notable Adverse Reactions: In the DB AD study, a 93-year-old AD patient with a history of IBS and intermittent diarrhea, along with multiple cardiac abnormalities including left ventricular hypertrophy, expired due to a GI bleed following 28 days of Axona administration. Also in the DB AD study, an 87-year-old patient with a history of diverticulitis and stomach ulcer was found to have a guaiac-positive stool when hospitalized for pneumonia. This patient was discharged from hospital without sequelae. All of these events were likely to be related to the subjects' underlying comorbidities; however, the possibility that Axona may exacerbate pre-existing GI inflammatory processes should be considered.

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 (see Section 5 "Warnings and Precautions"). 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.

7. Drug Interactions
Subjects enrolled in the AD trial 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. Approximately 80% of the patients in this trial were receiving one or more medications for AD (cholinesterase inhibitors and NMDA receptor antagonists), with a higher proportion of subjects within the placebo group receiving these medications compared with the Axona group. Despite being tested in a non-naïve population, Axona resulted in significant improvement in the ADAS-Cog test in E4(–) AD patients relative to placebo. Therefore, Axona can be administered as adjunctive therapy along with other AD medications.

8. Use in Specific Populations
Axona has been tested in clinical studies of normal elderly subjects, and patients with 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 (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.

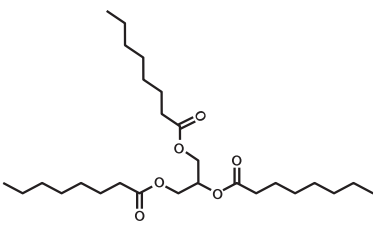
9. Drug Abuse and Dependence
Axona does not induce dependency and is not a candidate for abuse.

10. Overusage
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.[14] 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.

11. Description

Ingredients
Axona consists primarily of a proprietary formulation of >95% pure semisynthetic caprylic triglyceride.

Structure of Caprylic Triglyceride
Caprylic triglyceride is an MCT that is Generally Recognized As Safe (GRAS, 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. MCTs are currently used in medical nutrition products for prolonged enteral support and malabsorption, refractive epilepsy, and in sports nutrition (as dietary supplements).



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

Ingredient List in Descending Order of Quantity by Weight
Caprylic Triglyceride, Potassium Caseinate (milk-derived protein), Maltodextrin, Whey Protein (milk-derived), Sugar, Sunflower Oil, Dimagnesium Phosphate, Tricalcium Phosphate, Dipotassium Phosphate, Soy Lecithin, Distilled Monoglyceride. Contains less than 2% of: Silicon Dioxide, Natural Vanilla Bean Extract, Sucralose, Acesulfame Potassium.

Nutritional content for each 40 g packet (as manufactured): total calories (217), protein (8 g), carbohydrate (7 g),* caprylic triglyceride (20 g), calcium (240 mg), potassium (255 mg), sodium (58 mg), phosphorus (363 mg), magnesium (116 mg).
*Total carbohydrates include 2 g sugar and a negligible amount of lactose.

Medical Food Category
A medical food is an official FDA product classification, which is formulated to be consumed or administered enterally (or orally) under medical supervision, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." This statutory definition was subsequently incorporated into the Nutrition Labeling and Education Act of 1990 and further incorporated and interpreted by FDA regulations and guidance documents.‡

Axona has been developed, manufactured, and labeled in accordance with both the statutory and FDA regulatory definition of a medical food, and pursuant to FDA guidance for industry. Axona is formulated for oral administration, for use under medical supervision and is intended specifically for the dietary management of the metabolic processes and nutritional requirements associated with mild to moderate AD.

12. Clinical Pharmacology—Mechanism of Action/Metabolism

Axona provides a simple and safe method to induce hyperketonemia, 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.[15] MCFAs enter the liver mitochondria as acyl-CoA, where they undergo β-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, ie, 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[16,17] until circulating concentrations reach approximately 12 mM, at which point they saturate the oxidative machinery.[18] 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.

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.[19]

13. 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 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.

14. Clinical Studies

Axona has been tested in 3 clinical trials in populations of patients with a diagnosis of probable mild to moderate AD and MCI, as well as in normal elderly volunteers.§

Single-Administration Clinical Study in Patients With AD or MCI[12]

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 MCTs 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 MCTs 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 (as described in Section 1 above) 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[13]

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

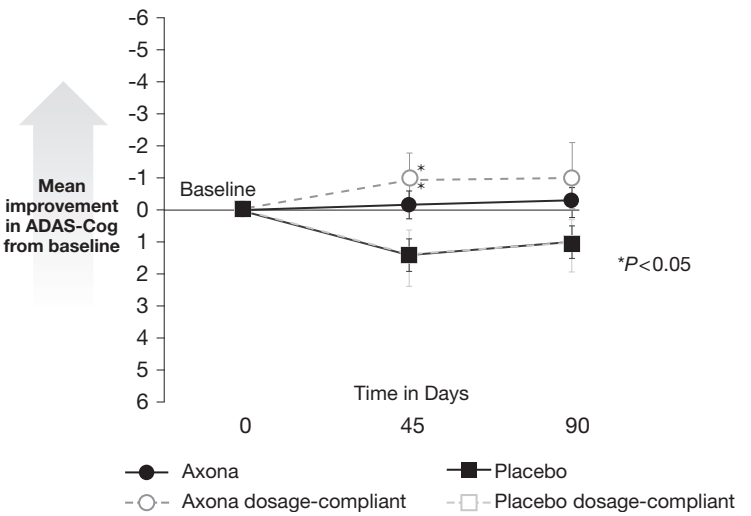
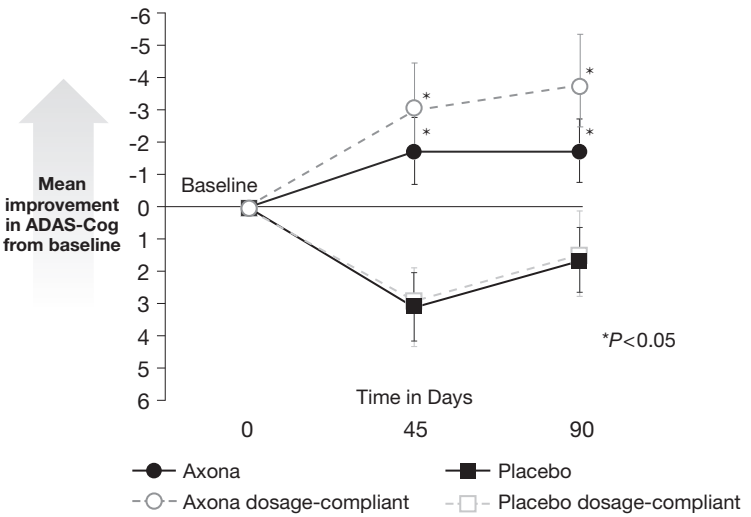


Figure 2: Significant improvements in ADAS-Cog for ApoE4(–) patients



A total of 49 patients who completed the 90-day DB phase of the study enrolled in the 6-month OL extension. Since the OL phase did not include an active control group, the significance of efficacy results was not determinable.

Bridging Study in Normal Elderly Volunteers
The third clinical study was an open-label, randomized bridging study in 66 normal elderly volunteers to establish the tolerability, safety, and pharmacokinetic (PK) profile of 3 different formulations of Axona administered for 14 days either with a 7-day titration (7 days at 10 grams MCTs followed by 7 days at 20 grams MCTs) or without titration (14 days at 20 grams MCTs). The original formulation of Axona used in the AD controlled clinical trial required reconstitution with a "meal replacement drink," such as Ensure®, in order to enhance product tolerability. The 2 new formulations tested each contained an identical amount of MCTs as the original formulation, but different amounts of proteins and carbohydrates, and allowed for reconstitution in 4-8 ounces of water. The highest mean BHB levels (C_{max}) and area-under-the-curve (AUC) values were observed in the cohort of subjects receiving the high-protein formulation at the 20-gram MCT level. This cohort of subjects receiving the high-protein formulation at the 20-gram MCT level also experienced the latest onset of most GI AEs. This is the formulation of Axona selected for marketing.

15. References

1. Hoyer S. Oxidative energy metabolism in Alzheimer brain. Studies in early-onset and late-onset cases. *Mol Chem Neuropathol*. 1992;16(3):207-224.
2. Small GW, Ercoli LM, Silverman DH, et al. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc Natl Acad Sci USA*. 2000;97(11):6037-6042.
3. Henderson ST. Ketone bodies as a therapeutic for Alzheimer's disease. *Neurotherapeutics*. 2008;5(3):470-480.
4. Costantini LC, Barr LJ, Vogel JL, Henderson ST. Hypometabolism as a therapeutic target in Alzheimer's disease. *BMC Neuroscience*. 2008;9(suppl 2):S16.
5. Parsons MW, Gold PE. Glucose enhancement of memory in elderly humans: an inverted-U dose-response curve. *Neurobiol Aging*. 1992;13(3):401-404.
6. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J. Effect of hyperketonemia and hyperlacticacidemia on symptoms, cognitive dysfunction, and counterregulatory hormone responses during hypoglycemia in normal humans. *Diabetes*. 1994;43(11):1311-1317.
7. Hasselbalch SG, Madsen PL, Hageman LP, et al. Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. *Am J Physiol*. 1996;270(5 Pt 1):E746-E751.
8. Izumi Y, Ishii K, Katsuki H, Benz AM, Zorumski CF. β-Hydroxybutyrate fuels synaptic function during development. Histological and physiological evidence in rat hippocampal slices. *J Clin Invest*. 1998;101(5):1121-1132.
9. Gasior M, Rogawski MA, Hartman AL. Neuroprotective and disease-modifying effects of the ketogenic diet. *Behav Pharmacol*. 2006;17(5-6):431-439.
10. Van der Auwera I, Wera S, Van Leuven F, Henderson ST. A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutr Metab (Lond)*. 2005;2:28.
11. Sucher KP. Medium chain triglycerides: a review of their enteral use in clinical nutrition. *Nutr Clin Pract*. 1986;1(3):146-150.
12. Reger MA, Henderson ST, Hale C, et al. Effects of β-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol Aging*. 2004;25(3):311-314.
13. Henderson ST, Vogel JL, Barr LJ, et al. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond).* 2009;6:31.
14. Traul KA, Driedger A, Ingle DL, Nakhasi D. Review of the toxicologic properties of medium-chain triglycerides. *Food Chem Toxicol*. 2000;38:79-98.
15. Bach AC, Babayan VK. Medium-chain triglycerides: an update. *Am J Clin Nutr*. 1982;36(5):950-962.
16. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab Res Rev*. 1999;15(6):412-426.
17. Morris AA. Cerebral ketone body metabolism. *J Inherit Metab Dis*. 2005;28(2):109-121.
18. Mayes PA. Oxidation of fatty acids: ketogenesis. In: Murray RK, Granner DK, Mayes PA, Rodwell VW, eds. *Harper's Biochemistry*. New York, NY: McGraw-Hill; 2000.
19. St-Onge MP, Bosarge A, Goree LL, Darnell B. Medium chain triglyceride oil consumption as part of a weight loss diet does not lead to an adverse metabolic profile when compared to olive oil. *J Am Coll Nutr*. 2008;27(5): 547-552.

16. How Supplied/Storage and Handling
Axona is supplied as a powder in individual packets of 40 grams (containing 20 grams MCTs). In addition, to facilitate patients' gradual acclimation to the full dose of Axona, 10-gram packets (containing 5 grams MCTs) are also available as professional samples. 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. Reconstituted product may be refrigerated and stored for up to 24 hours. Refrigerated product should be re-blended and thoroughly mixed prior to consumption.

Storage: Axona should be stored at room temperature, 15°C-30°C (59°F-86°F), sealed, and protected from light and moisture.

17. Patient Counseling Information
Axona is a medical food product and must be used under medical supervision. Both the patients and their 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.

Starting Axona
It is recommended that patients start Axona using a graduated dosing regimen. During the first week of product administration, patients should start with 1 tablespoon (~8-10 g) daily for 2 days, and increase the dose by 1 tablespoon (~8-10 g) every other day as tolerated until the full dose (~5 tablespoons/40g) is taken. Axona should always be taken following a full meal. Professional samples in 10 g packets are available.

Axona Graduated Dosing Plan

	Sample Kit		No Sample Kit
Day 1	1 packet	10 g	1 tablespoon
Day 2	1 packet	10 g	1 tablespoon
Day 3	2 packets	20 g	2 tablespoons
Day 4	2 packets	20 g	2 tablespoons
Day 5	3 packets	30 g	3 tablespoons
Day 6	3 packets	30 g	3 tablespoons
Day 7	4 packets	40 g	4 tablespoons
Day 8 (and beyond)	Fill 40-g packets and take as directed		

Taking Axona
The therapeutic dose of Axona (one packet/40g) should be taken once a day 15-30 minutes following a full meal (preferably breakfast or lunch, whichever is more substantial).

A small minority of patients appear to be more sensitive 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 dose.

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 can 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.

Over-the-counter medications such as simethicone, antacids, and antidiarrheals also can be useful for treating mild to moderate GI side effects. Patients should seek the advice of their healthcare provider if symptoms persist.

† 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 Accera, Inc.

‡ Definitions and official FDA information about medical foods are found at: 21 U.S.C. sec. 360ee(b) (3), 21 C.F.R. sec. 101.9 (j)(8), and "Guidance for Industry: Frequently Asked Questions About Medical Foods" (May 2007), FDA website.

§ Further information on these clinical trials may be found at www.about-axona.com

Rx only.

Manufactured for:
Accera, Inc.
380 Interlocken Crescent, Suite 780
Broomfield, CO 80021
USA
1-877-649-0004

For more information, visit www.about-axona.com.

Patents issued: USP 6,835,750, EP 1292294, and JP 3486778; and patents pending.

LB-104.9.0