**Product Code**

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Usage</th>
</tr>
</thead>
</table>
| 42907-040-30 | By oral route for each 40-g packet (as manufactured) | total calories (217), protein (8 g), carbohydrate (7 g), caprylic triglyceride (30 g), calcium (240 mg), and vitamin D3 (400 IU). *Total carbohydrates include 2 g of sugar and a negligible amount of lactose.

**Ingredient List in Descending Order of Quantity by Weight**

- Whey Protein (milk-derived), Sugar, Sunflower Oil, Dimagnesium Phosphate, Calcium Carbonate, Soy Lecithin, Distilled Monoglycerides. Contains less than 2% of: Silicon Dioxide, Natural Vanilla Bean Extract, Sucrose, Ascorbic Acid.

- Nutritional content for each 40 g packet (as manufactured): total calories (217), protein (8 g), carbohydrate (7 g), caprylic triglyceride (30 g), calcium (240 mg), and vitamin D3 (400 IU). *Total carbohydrates include 2 g of sugar and a negligible amount of lactose.

**Adverse Events Reported in ≥3% of Axona Patients**

<table>
<thead>
<tr>
<th>Any Event</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Urinary tract infection</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Hypertension</td>
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<td>3</td>
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<td>Alopecia</td>
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<td>Rhinitis</td>
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<td>3</td>
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<tr>
<td>Coughing</td>
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<td>3</td>
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<td>2</td>
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</tbody>
</table>

**Hypometabolism**

**Hypometabolism** may not be solely an artifact of cell atrophy since it occurs in asymptomatic patients at risk for AD, as well as in familial forms of AD. Thus, this is a disease with distinctive metabolic and nutritional requirements.

- **Hypometabolism** is characterized by a concomitant reduction in key metabolic pools, including glycolytic intermediates (e.g., fructose-1,6-bisphosphate), gluconeogenic (e.g., lactate), and ketogenic (e.g., acetoacetate) intermediates. This concomitant hypometabolism may be related to a decrease in the visceral fat mass, which is a major metabolic organ, especially since visceral fat and total body fat are positively correlated with circulating insulin levels and are associated with the metabolic syndrome. The decrease in visceral fat may contribute to the metabolic abnormalities observed in AD patients, particularly the decrease in ketogenesis.

**Ketogenes**

Ketogenesis is a process by which the body produces ketones from the breakdown of fatty acids, mainly from the breakdown of triglycerides. Ketones are a type of fuel that can be used by the brain and other tissues when glucose is not available, such as during fasting or in patients with diabetes. In AD, ketogenesis is increased as a compensatory mechanism to maintain energy supply to the brain.

- **Ketogenesis** occurs in the liver, primarily through the degradation of ketone bodies (acetone, acetoacetate, and beta-hydroxybutyrate) that are produced by the breakdown of fatty acids. These ketone bodies can be oxidized by the brain to provide energy, thereby reducing the reliance on glucose, which is a limiting factor in AD patients due to the decrease in glucose metabolism.

**Ketone Bodies**

Ketone bodies are a group of organic compounds produced by the liver from fatty acids and released into the bloodstream. They include acetone, acetoacetate, and beta-hydroxybutyrate. These ketone bodies can be metabolized by the brain to generate energy, providing an alternative fuel source.

- Acetone is a colorless, volatile, flammable liquid.
- Acetoacetate is a ketone body that is formed from the breakdown of fatty acids and can be metabolized by the liver to produce energy.
- Beta-hydroxybutyrate is another ketone body that is produced by the liver and can be used as a fuel by the brain.

**Ketose**

Ketose is a ketone body that is produced by the liver from the metabolism of fatty acids.

- Ketose is a ketone body that is produced by the liver from the metabolism of fatty acids. It is a precursor of ketone bodies and can be metabolized by the liver to produce energy.

**Ketoderivatives**

Ketoderivatives are compounds that are derived from ketone bodies and can be used as fuel by the body. They include ketone bodies themselves, such as acetone, acetoacetate, and beta-hydroxybutyrate, as well as other ketone bodies, such as ketones, ketodiesters, and ketones.

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**Ketogenic Diet**

A ketogenic diet is a very low-carbohydrate, high-fat diet that is used to induce ketosis, a state in which the body relies on ketones as its primary source of energy. Ketosis can be achieved by drastically reducing carbohydrate intake and increasing fat consumption. The ketogenic diet has been shown to improve symptoms in people with certain neurological disorders, such as epilepsy.

- Ketosis is a state in which the body relies on ketones as its primary source of energy. It is typically achieved by drastically reducing carbohydrate intake and increasing fat consumption.

**Cognitive Function**

Cognitive function is the ability to think, learn, and act, and it is closely related to metabolism. In AD, cognitive function is impaired due to the loss of neurons and the deposition of amyloid plaques and neurofibrillary tangles.

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**Memory Loss**

Memory loss is a common symptom of AD, and it is typically associated with the impairment of cognitive function. In AD, memory loss is characterized by the inability to remember recent events, such as recent appointments or family members' names.

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Clinical Study in Patients With Probable Mild to Moderate AD
The second clinical study was a DB, randomized, 90-day study with a 2-week washout period at multiple US clinical centers in a total of 101 patients meeting the National Institute on Aging-Alzheimer’s Association (NIA-AA) criteria for probable AD. Patients were randomized to receive Axona or placebo. At day 45, ADAS-Cog scores stabilized in the Axona group, whereas the decline in cognition was observed in the placebo group. The point difference in ADAS-Cog change from baseline at day 45 between groups was (P = 0.004) (see Figure 1). The point difference in ADAS-Cog change from baseline at day 90 between groups was 1.54 (P = 0.067). Final ADAS-Cog evaluations were performed after 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 in ADAS-Cog change from baseline at day 104 was not statistically significant (P = 0.406).

As defined in the Study (Statistical Plan), the ADAS-Cog change from baseline score was evaluated in subgroups of patients based on APOE4 genotype. The APOE+4 patients receiving Axona showed improved cognitive function when compared with APOE+4 patients receiving placebo (n = 23, Axona; n = 26, placebo). The point difference in change from baseline ADAS-Cog scores for Axona vs. placebo and patients at day 45 was 2.56 points (P = 0.005), and was 3.36 at day 90 (P = 0.015; see Figure 2). In APOE+4 patients (n = 31 vs. Axona; n = 31, placebo), change in ADAS-Cog total scores for the 2 groups was essentially identical at all time points, with no patients showing decline rather than improvement at day 45 and 90. Additionally, a smaller proportion of patients who were dosage compliant (defined as patients who reported consuming at least 80% of the total intended number of capsules) in each of the study groups had a greater difference 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 was 3.96 at day 45 (P = 0.001) and 4.30 at day 30 [P = 0.006] (see Figure 3). Among 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
A total of 48 patients who completed the 90-day DB phase of the study entered into a 6-month OL extension. Treatment of those patients was continued with Axona. The clinical benefits of a DB control group were statistically significant and the efficacy results were not determinable.

Clinical Study in Normal Elderly Volunteers
The third clinical study was an open-label, randomized bridging study in 66 healthy volunteers (n = 38, Axona; n = 31, placebo) aged 55-85 years and weighing 55-90 kilograms. The study was designed to evaluate the safety and tolerability of Axona in healthy elderly volunteers, and to determine the maximum recommended oral dose of Axona. The prescribed daily exposure of Axona will be 0.29 grams/kg/day in a 70-kg patient for up to 90 days. The prescribed daily exposure of Axona will be 0.29 grams/kg/day in a 70-kg patient for up to 90 days.

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