KetoVie™ 3:1 (Low carbohydrate MCT enhanced lipid-based ketogenic formula)

PRODUCT INFORMATION

KetoVie 3:1 Unflavored 250 mL carton (8.5 fl. oz) Reimbursement Code: 24359-0504-03
Manufactured by Ajinomoto Cambrooke, Inc. Ayer, MA 01432 www.cambrooke.com

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DISPENSE BY PRESCRIPTION

KetoVie 3:1 is a nutritionally complete medical food for the dietary management of intractable epilepsy, glucose transporter type 1 deficiency syndrome, pyruvate dehydrogenase deficiency and other disorders where a ketogenic diet is indicated.

DESCRIPTION

KetoVie 3:1 is a liquid ready to use prescription medical food for the clinical dietary management of intractable epilepsy, glucose transporter type 1 deficiency syndrome (Glut-1 DS), pyruvate dehydrogenase deficiency (PDH) and other disorders that require a ketogenic diet. KetoVie 3:1 is to be used only under medical supervision. KetoVie 3:1 has been developed, labeled and should be administered in accordance with the statutory and the Food and Drug Administration's (FDA's) regulatory definition of Medical Foods. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as a formulation to be administered enterally (for oral or tube feeding) under the supervision of a physician 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. 21 U.S.C. 360ee(b)(3).

KetoVie 3:1 is supplied in a single dose, 8.5 fl oz (250 mL) cartons, 30 cartons per case. Each carton contains a 3:1 ketogenic ratio (3 grams of fat to every 1 gram of non-fat [protein and net carbohydrate*]), 260 calories, 100% whey protein source, 20% of total calories as medium chain triglyceride (MCT), and provides a complete micronutrient profile with enhanced amounts of selenium and carnitine. The caloric density (calories per mL) of KetoVie 3:1Unflavored is 1 kcal/mL.

**The net carbohydrate weight (g) is the total carbohydrate minus the total dietary fiber.*

PRIMARY INGREDIENTS

Ready to Use 3:1 Ketogenic Ratio

KetoVie 3:1 contains a 3:1 macronutrient ratio by weight of fat to combined protein and net carbohydrate* weight. The classic ketogenic diet is effective in the dietary management of intractable epilepsy[1,2,3,4,5] and is considered the diet of choice for the metabolic disorders glucose transporter type 1 deficiency syndrome (Glut-1 DS)[6,7,8] and pyruvate dehydrogenase deficiency (PDH).[8,9]

Benefits of a liquid ready to use ketogenic medical food, such as KetoVie 3:1, whether as sole source enteral nutrition by a feeding tube or oral supplemental nutrition, include palatability, ease of diet titration, reduced risk of calculation and preparation error, and improved compliance.[10, 11]

Fat and Medium Chain Triglycerides

KetoVie 3:1 contains a blend of saturated fats, polyunsaturated fats and monounsaturated fats. Refer to the Fat Profile Table below for a more detailed breakdown. KetoVie 3:1 has a saturated fat component with over 65% contribution from medium chain triglycerides (MCTs). MCTs are fats with 6-12 carbon length fatty acid chains. MCTs can be beneficial to ketogenic diet management in that it is directly absorbed in the intestines and more efficiently processed into ketones in the liver compared to long chain triglycerides (LCTs). MCTs also have a laxative effect, which can be helpful for bowel regularity.[12] Algae-sourced long chain omega three fatty acid docosahexaenoic acid (DHA) and arrachidonic acid (ARA) is added at 93 milligrams per serving and KetoVie 3:1 is additionally supplemented with essential fatty acids linoleic and α-linolenic acid.

FAT PROFILE		
	Measurement per 250mL serving	**KetoVie 3:1 Unflavored**
Total Fat	grams	25.1
Saturated Fat	grams	9.3
MCT	grams	6.0
Monounsaturated Fat	grams	10.8
Polyunsaturated Fat	grams	4.2
Linoleic Acid	milligrams	3530
α-Linolenic Acid	milligrams	650
DHA	milligrams	93
ARA	milligrams	93

Whey

KetoVie 3:1 protein source is from a 100% whey protein. Whey protein is a complete protein derived from milk. Cow and human milk contain both whey and casein protein fractions. Whey

protein has been shown to improve gastric emptying time in those with poor gastric motility compared to casein dominant milk proteins.[13,14] Impaired gastric motility can be common for those on a ketogenic diet.[8]

Carnitine
Carnitine is a conditionally essential amino acid necessary for transporting fatty acids into the mitochondria of cells for oxidation and is crucial for energy and ketone production. Carnitine deficiency is common among children and adolescents with epilepsy, especially among those receiving valproic acid therapy, a common medication used to treat seizures.[15,16] KetoVie 3:1 contains 33 mg of carnitine per serving.

Selenium
Selenium is an essential trace element with many critical roles in the body. Selenium deficiency has been associated with ketogenic therapy. A serious complication of selenium deficiency is cardiomyopathy, which can be fatal.[17] Intakes of at least 20 mcg per day of selenium have been found to be protective against selenium deficiency related cardiomyopathy in adults.[18] KetoVie 3:1 contains 15 mcg of selenium per serving. The Recommended Dietary Allowance (RDA) of selenium is 15-55 mcg per day depending on age with upper limits ranging between 45-400 mcg per day.[18]

Fiber
One of the most common complications related to ketogenic diet therapy is gastrointestinal (GI) disturbance, involving nausea/vomiting, diarrhea, and/or constipation. Because ketogenic diets restrict carbohydrates, it may be difficult to meet dietary fiber recommendations. KetoVie 3:1 contains the soluble, prebiotic fibers fructooligosaccherides (FOS) and galactooligosaccherides (GOS), which help support digestive health and immunity[19].

Dietary Fibers	grams
Total	1
Soluble	1
Insoluble	0

Micronutrients and Macronutrients
Patients utilizing ketogenic therapy follow a severely restricted diet to minimize carbohydrate intake and provide the necessary fats at the desired ketogenic ratio for the production of ketone bodies. As such, there is meaningful risk and challenges in receiving recommended daily intake of many nutrients.[20] Many commercially available vitamin and mineral supplements also contain carbohydrate which must be factored into the diet. To compensate for this, KetoVie 3:1 includes a full profile of micronutrients and macronutrients, as well as the enhanced levels of selenium and carnitine as noted above. With a documented potential risk of bone fractures[21] when on ketogenic therapy along with the challenge of meeting recommended micronutrients noted above, the formulation of KetoVie 3:1 contains a special blend of vitamins and minerals important for bone health including: Vitamin D3, calcium, phosphorus, magnesium, and Vitamin K.

The use of oral citrates has been shown to be an effective preventative supplement against kidney stones (renal calculi) in children who receive the ketogenic diet.[22] KetoVie 3:1 contains citrates (potassium citrate and sodium citrate) at 10 mEq per serving.

Free of Sugar Substitutes
KetoVie 3:1 Unflavored does not contain any artificial sweeteners or sugar substitutes.

Water
KetoVie 3:1 Unflavored contains 85% free water.

Complete Ingredients
Water, high oleic canola oil, whey protein concentrate, medium chain triglycerides, less than 2% of galactooligosaccherides (GOS), fructooligosaccherides (FOS), canola oil, vitamin A palmitate, cholecalciferol, dl-alpha-tocopheryl acetate, niacinamide, d-calcium pantothenate, phytonadione, folic acid, biotin, riboflavin, sodium ascorbate, thiamin mononitrate, pyridoxine hydrochloride, choline bitartrate, cyanocobalamin, potassium chloride, magnesium phosphate, calcium phosphate, potassium hydroxide, potassium phosphate, ferric pyrophosphate, zinc gluconate, potassium iodide, sodium selenite, copper gluconate, sodium molybdate, manganese sulfate, chromium chloride, calcium citrate, citric acid ester of mono and di-glycerides, potassium citrate, DHA algal oil, ARA fungal oil (M. alpina), mono and diglycerides, salt, L-carnitine, taurine, inositol. Contains milk.

Low in lactose (0.32g/250mL serving).

GENERALLY RECOGNIZED AS SAFE
The ingredients in KetoVie 3:1 are Generally Recognized As Safe (GRAS). This is the statutory safety standard of the U.S. Food and Drug Administration (FDA). The use of an ingredient may be established as GRAS based on documented widespread common use of the ingredient in foods prior to January 1, 1958, or based on scientific procedures. GRAS status based on scientific procedures requires technical evidence of safety (i.e., a reasonable certainty of no harm under the conditions of intended use), and evidence of general recognition of such safety amongst qualified experts.

MEDICAL FOOD STATUS

KetoVie 3:1 has been developed, labeled and should be administered in accordance with FDA statutory and regulatory definition of Medical Foods. Congress defines "Medical Food" in the Orphan Drug Act and Amendments of 1988 as a formulation to be administered enterally (for oral or tube feeding) under the supervision of a physician 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.

INDICATIONS FOR USE

For the dietary management of intractable epilepsy, glucose transporter type 1 deficiency syndrome (Glut-1 DS), pyruvate dehydrogenase deficiency (PDH) and other disorders where a ketogenic diet is indicated. KetoVie 3:1 should always be used under medical supervision. KetoVie 3:1 may be used as an oral supplement or as sole source enteral nutrition via a feeding tube.

AMOUNT OF KETOVIE 3:1 NEEDED TO MEET 100% MICRONUTRIENT NEEDS*	
Age (years)	**Amount**
1-3	600 mL (624 kcal)
4-8	865 mL (900 kcal)
9-13	1500 mL (1560 kcal)
Older children and adults	Varies based on age and gender

**Excludes electrolytes*

CLINICAL EXPERIENCE

Ketogenic diet therapy has been used in the treatment of seizures since 1921. There has been a resurgence in its use in recent years.[23] Several recent meta-analysis reviews have looked at ketogenic diet therapy and have shown that ketogenic diet therapy is an effective treatment in reducing the number of seizures in children with intractable seizures, though not every patient will respond.[4,5,24] One of the meta analysis studies pooled data from over 1,084 pediatric epileptic patients and found the ratio of treatment success (>50% seizure reduction) to diet discontinuation was 2.25 (95% confidence interval 1.69-2.98), indicating a high level of efficacy for ketogenic diet therapy and seizure reduction.[5] A 2008 randomized control trial of 145 children and adolescents with intractable epilepsy found 38% of patients achieved >50% reduction of seizures after 3 months of ketogenic diet therapy compared to controls. Another 7% achieved >90% reduction in seizures.[1] Adolescent and adult data indicate ketogenic diet therapy to be equally efficacious in these groups.[2,4] There are studies showing benefit of ketogenic diet therapy to several different seizure types and other conditions.[8,25]

Conditions Shown to Respond to Ketogenic Diet Therapy

- Glucose transporter protein 1 (GLUT-1) deficiency
- Pyruvate dehydrogenase deficiency (PDHD)
- Myoclonic-astatic epilepsy (Doose syndrome)
- Tuberous sclerosis complex
- Rett syndrome
- Severe myoclonic epilepsy of infancy (Dravet syndrome)
- Lennox Gastaut syndrome
- Infantile spasms
- Selected mitochondrial disorders
- Glycogenosis type V
- Landau-Kleffner syndrome
- Lafora body disease
- Subacute sclerosing panencephalitis (SSPE)

PHARMACOKINETICS

Ketogenic diet therapy is meant to put the body into a state of ketosis by using ketone bodies for energy. Ketone bodies are the by-product of fat metabolism and can be used as an alternative to glucose as a fuel source for the brain. Ketosis is brought about by the oxidation of body fat stores, such as during times of prolonged fasting, or when the body is fed a diet primarily made up of fats. KetoVie 3:1 is a specially formulated ketogenic medical food at a classic 3:1 ketogenic ratio (4 grams of fat to every 1 gram of non-fat [protein and net carbohydrate.]) This 3:1 ketogenic ratio has been found to be effective in achieving the desired level of ketosis.[8] Fats are metabolized in a metabolic pathway known as beta oxidation. In this multi-step process, fatty acids are taken up by cells and transported into the mitochondria by a carnitine shuttle, hence carnitine's important role in fatty acid metabolism. In the mitochondria, the activated fatty acids are converted into acetyl-CoA. Acetyl-CoA can then be further processed into energy via the tricarboxylic acid cycle (TCA cycle) or taken to the liver to be turned into ketone bodies. Ketone bodies can pass through the blood brain barrier and may play a role in ketogenic diet therapy's suppression of seizure activity in the brain. Included in the KetoVie 3:1 formulations are 20% of calories from medium chain triglycerides (MCTs). MCTs are fats with 6-12 carbon length fatty acid chains. MCTs are particularly beneficial to achieving the desired level of ketosis in the body as they are absorbed directly from the intestines and sent directly to the liver for efficient processing into ketone bodies.[12]

Precautions and Contraindications

KetoVie 3:1 contains protein from whey, a milk protein; therefore, it may not be suitable for those with an allergy to milk or milk products. There are certain conditions in which a ketogenic diet may be contraindicated. These may include, but are not limited to, the conditions listed below.[8]

Conditions Contraindicated to Use of Ketogenic Diet Therapy

Adverse Reactions

- Carnitine deficiency (primary)
- Carnitine palmitoyltransferase (CPT) I or II deficiency
- Carnitine translocase deficiency
- Beta-oxidation defects
- Medium-chain acyl dehydrogenase deficiency (MCADD)
- Long-chain acyl dehydrogenase deficiency (LCADD)
- Short-chain acyl dehydrogenase deficiency (SCADD)
- Long-chain 3-hydroxyacyl-CoA deficiency
- Medium-chain 3-hydroxyacyl-CoA deficiency
- Pyruvate carboxylase deficiency
- Porphyria
- Inability to maintain adequate nutrition
- Noncompliance

There are no known incremental adverse reactions for the use of KetoVie 3:1 as a part of a ketogenic diet. Ketogenic diets have been associated with certain adverse reactions. These can include metabolic abnormalities, gastrointestinal distress (vomiting, constipation, diarrhea, abdominal discomfort,) secondary carnitine deficiency, hypercholesterolemia, renal calculi, delayed linear growth in children and increased risk of bone fractures.[3,25,26,27, 28, 29] Close medical supervision is required.

Drug Interactions

KetoVie 3:1, when prescribed as supplemental or sole source nutrition, may impact how some drugs are metabolized. All medications should be discussed with a physician or pharmacist. Medical supervision by a physician is required.

Toxicity

None known.

SPECIAL POPULATIONS

KetoVie 3:1 is indicated for patients 12 months and older requiring a ketogenic diet. Always check with physician for proper dosage recommendations.

DOSAGE AND ADMINISTRATION

Use as directed by physician. Must be administered under medical supervision only. Ready to drink as an oral supplement or administer via a feeding tube for sole source enteral nutrition. Shake well. Store in a cool, dry place. Refrigerate after opening and store refrigerated up to 24 hours. Once opened, product should be kept for no longer than 4 hours at room temperature. Do not freeze.

HOW SUPPLIED

KetoVie 3:1 Unflavored is supplied in a single dose, 8.5 fl oz (250 mL) cartons, 30 cartons per case. Keep in a cool, dry place until ready to use. Reimbursement Code: 24359-0504-03.

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