

# UltraMeal® Plus 360° Medical Food PharmaSoy®-Based Powder with Plant Sterols and a Blend<sup>†</sup> of RIAA and Acacia for Oral Administration. Dispensed By Healthcare Practitioner Recommendation.

(<sup>†</sup>Patent pending. Also contains Metafolin®, a body-ready, nature-identical folate: U.S. Patents 5,997,915 and 6,254,904.)

## INDICATIONS AND USAGE

UltraMeal Plus 360° is a nutritionally fortified, soy-based medical food indicated for individuals with metabolic syndrome and cardiovascular disease (CVD) issues, such as hypertension, hypercholesterolemia, and hypertriglyceridemia.

While lifestyle factors strongly influence the development of these conditions, research has also implicated abnormal inflammatory processes in the development of insulin resistance and metabolic syndrome, such as the production of the pro-inflammatory cytokines interleukin-1 beta (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interferon gamma (IFN- $\gamma$ ).<sup>1-3</sup> Because IL-1 $\beta$ , TNF- $\alpha$ , and IFN- $\gamma$  are under nuclear factor kappa B (NF- $\kappa$ B) control, modalities that regulate NF- $\kappa$ B expression may be expected to have a beneficial effect on insulin resistance.

UltraMeal Plus 360° provides specialized, multi-mechanistic nutritional support designed to be used as part of a comprehensive lifestyle intervention therapy (i.e., complementary diet and exercise program), and has been recommended for daily use with no serious adverse events reported.

## DESCRIPTION

UltraMeal Plus 360° (in a powdered form) is a medical food formulated with soy protein, plant sterols, and a proprietary blend of a modified extract of rho-iso-alpha acids (RIAA) from *Humulus lupulus L.* (hops) and *Acacia nilotica* extract, along with targeted foundation nutrients for those with CVD and metabolic syndrome.

Groundbreaking research suggests that certain food components can selectively modify kinase activity in favor of good health—referred to as selective kinase response modulators (SKRMs). Established protein and genomic testing technologies\* and clinical evaluations\*\* demonstrate that RIAA and acacia act as SKRMs to modulate specific kinases in adipocytes (fat-storing cells) involved in glucose utilization and insulin signaling—inhibiting the major upstream inflammation-regulating event (NF- $\kappa$ B induction) that plays a critical role in insulin resistance. Balanced kinase signaling also helps to maintain healthy blood glucose and triglyceride (TG) levels, an important suggestive indicator of metabolic syndrome.

In addition, soy protein and plant sterols have been recognized by the U.S. Food and Drug Administration (FDA) and National Institutes of Health (NIH)

for their roles in promoting cardiovascular (CV) health. Clinical testing with UltraMeal Plus 360° ingredients demonstrates that the combination of these key nutrients, along with other supportive nutrients, may provide greater support for CVD issues than a healthy diet and exercise alone.

## Each serving (51 g) supplies (Natural Vanilla Flavor):

Calories 165, Fat 3 g (Saturated Fat<sup>†</sup> 1 g, Trans Fat 0 g), Cholesterol 0 mg, Sodium (as sodium chloride) 290 mg, Potassium (as potassium chloride and potassium iodide) 500 mg, Carbohydrate 23 g (Dietary Fiber 4 g, Sugars 16 g), Protein<sup>††</sup> 15 g, Vitamin A (as retinyl palmitate) 1,750 IU, Vitamin C (as ascorbic acid) 60 mg, Calcium (as dicalcium phosphate) 600 mg, Iron (as ferrous fumarate) 3 mg, Vitamin D (as cholecalciferol) 40 IU, Vitamin E (as d-alpha tocopheryl acetate) 11 IU, Thiamin (as thiamin HCl) 0.75 mg, Riboflavin 0.85 mg, Niacin (as niacinamide) 10 mg, Vitamin B<sub>6</sub> as pyridoxine HCl) 25 mg, Folate (as folic acid and L-5-methyl tetrahydrofolate<sup>†††</sup>) 400 mcg, Vitamin B<sub>12</sub> (as cyanocobalamin) 30 mcg, Biotin 150 mcg, Pantothenic Acid (as D-calcium pantothenate) 5 mg, Phosphorus (as dicalcium phosphate) 500 mg, Iodine (as potassium iodide) 75 mcg, Magnesium (as magnesium citrate) 150 mg, Zinc (as zinc gluconate) 9 mg, Copper (as copper gluconate) 1 mg, Manganese (as manganese gluconate) 0.3 mg, Chromium (as chromium polynicotinate) 100 mcg, Isoflavones 17 mg, Plant Sterols (including beta-sitosterol and other plant sterols) 2,000 mg.

**Other Ingredients:** Soy protein isolate<sup>†</sup> (PharmaSoy<sup>®</sup>), fructose, soy fiber (soy), plant sterols (soy), inulin, natural flavors, olive oil, silica, proprietary blend of RIAA and acacia [magnesium salts of reduced iso-alpha acids (from hops extract, *Humulus lupulus L.*), hydrogenated soybean oil encapsulate, and acacia extract], lecithin (soy), cellulose gum, xanthan, and carrageenan. Contains: soy.

**Formulated to Exclude:** Wheat, gluten, yeast, dairy products, nuts, tree nuts, fish, shellfish, or artificial colors, sweeteners, or preservatives.\*\*\*

## MECHANISM OF ACTION

### RIAA & Acacia (SKRMs)—healthy insulin & blood lipids

RIAA and acacia are SKRMs demonstrated to positively influence fasting insulin and lipid parameters. Hops displays antioxidant and anti-inflammatory activity and has been demonstrated in third-party and proprietary research to selectively modify inflammatory mediators without suppressing mediators necessary to perform vital body functions.<sup>4,5</sup> Traditional medicine supports the use of acacia in diabetes and inflammatory disorders, and animal research has demonstrated its blood sugar-balancing properties and potential for human use.<sup>6</sup> Proprietary in vitro testing of these ingredients has demonstrated inhibition of IL-6 cytokines and NF- $\kappa$ B induction that influence insulin function. In addition, proprietary in vitro, animal and human studies have shown that RIAA and acacia improve fasting insulin and lipid parameters (see “IN VITRO AND ANIMAL TESTING” and “CLINICAL TESTING”).<sup>7</sup>

### Plant Sterols—healthy cholesterol levels

The National Cholesterol Education Panel (NCEP) of the NIH recommends the consumption of 2 grams of plant sterols daily, along with healthy eating and exercise, to reduce the risk of CVD. Studies have shown that 1.3 grams of plant sterols per day are needed to show a significant cholesterol-lowering effect. The FDA therefore states that “foods containing at least 0.65 grams

per serving of plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 grams, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.” One serving of UltraMeal Plus 360° supplies 2 grams of plant sterol esters.

#### **Soy Protein and Isoflavones**—*CVD risk reduction, body composition*

Soy protein and isoflavones may help improve body composition by promoting a healthy lean muscle mass.<sup>8,9</sup> Furthermore, the FDA states that “diets low in saturated fat and cholesterol that include 25 grams of soy protein a day may reduce the risk of heart disease.” UltraMeal Plus 360° provides 15 grams of soy protein per serving.

#### **Chromium**—*healthy blood glucose*

Preliminary evidence suggests that chromium may help reduce excess body fat and increase lean muscle mass, most likely due to its beneficial effects on glucose, insulin, and lipid metabolism.<sup>10,11</sup>

#### **B Vitamins, Folic Acid & Metafolin® (L-5-MTHF)**—*methylation, homocysteine metabolism, CV health*

Along with folate, vitamins B<sub>6</sub> and B<sub>12</sub> aid in homocysteine metabolism and other CV health aspects. Folate provides the one-carbon units necessary for methylation of a wide variety of biological substances, including homocysteine—which supports cholesterol metabolism and overall CV health.<sup>12</sup> Due to genetic variation in the activity of the folate metabolizing enzyme methylenetetrahydrofolate reductase (MTHFR), up to 40% of the population may not receive all the vital benefits expected from dietary folate or folate supplementation due to inefficient conversion to one of its biologically active forms—L-5-MTHF. As the form most used by the body, L-5-MTHF may be preferred for this large segment.<sup>13</sup>

#### **Other Vitamins and Minerals**—*overall health support*

UltraMeal Plus 360° provides high quality foundation nutrition for patients with CVD to support normal metabolic functioning and overall health.

#### **Low-Glycemic Load Diet**—*glucose/insulin function, CV health, inflammation reduction, body composition*

Similar to SKRMs, food consumption influences health through nutrient content and stimulates hormone release that affects signal transduction and genetic expression.<sup>14</sup> Postprandial spikes in blood glucose (common with high sugar/low fiber diets) adversely influence CV function through oxidative stress, inflammation, protein glycation, and procoagulant activity.<sup>15</sup> Glycemic index (GI, a measure of carbohydrate quality) and glycemic load (GL, which also considers carbohydrate quantity) are values assigned to foods that can be used to plan diets to help maintain glucose homeostasis. Prospective observational studies suggest that dietary GI and/or GL independently predict risk to CVD, and also suggest a link to the risk of obesity, diabetes, and hormone-related disorders.<sup>14,15</sup> Modified Mediterranean diets, typically based on whole foods with a lower GL, have been shown to improve postprandial glucose, lipids, inflammation, and CV health.<sup>16</sup> In clinical testing, UltraMeal Plus 360° was shown to have a low GI when

referenced against both white bread and glucose, which classifies it as a low-GI food considered to be beneficial for individuals with dysglycemia. Each serving of UltraMeal Plus 360° contains only 190 calories and is sweetened naturally with fructose, the form found in fruits and is a preferred sugar source to promote healthy blood sugar management.<sup>17</sup> A comprehensive patient guide for UltraMeal Plus 360° outlines the specifics of a complementary Mediterranean-style, low-GL diet and simple exercise regimen.

#### **IN VITRO AND ANIMAL TESTING**

*In Vitro.* Over 200 natural substances and extracts were tested for their influence on insulin responses in adipocyte cells. In early in vitro studies\* using the 3T3-L1 cell model system, an RIAA/acacia combination was shown to inhibit the induction of NF-κB, the major upstream inflammation-regulating event that plays a central role in insulin resistance. In vitro tests\* also demonstrated inhibition of IL-6 cytokines that influence insulin function.<sup>7</sup>

*Animal Models.* In subsequent animal studies\* using the diabetic mouse model (db/db), an RIAA/acacia combination reduced insulin levels by 20.2%, comparable to the efficacy of positive study controls. In the same animal model, this blend reduced TG and was comparable in efficacy to a leading conventional approach (Figure 1).<sup>7</sup>

#### **CLINICAL TESTING**

*Study #1: RIAA/Acacia.* RIAA and acacia were selected for further evaluation in a preliminary 8-week, randomized, placebo-controlled, double-blind trial\*\* with 91 subjects. The RIAA/acacia group showed a greater decrease in fasting insulin and 2-hour postprandial insulin levels, as well as a greater decrease in 2-hour postprandial blood glucose levels. Highlights of study results (all results versus the placebo group):

- 35 times greater statistically significant decrease in TG levels (-48.97 vs. -1.48) (Figure 2).
- Almost 5 times greater statistically significant decrease in homeostatic model assessment score (HOMA), a published measure of insulin resistance (-0.78 vs. -0.16 [(insulin (mIU/mL)\*glucose (mg/dL))/405]) (Figure 3).
- 3 times greater decrease in fasting insulin (-3.79 vs. -1.17 mIU/mL).
- 87% greater decrease in 2 h pp insulin (-29.81 vs. -15.98 mIU/mL).
- 44% lower level in fasting glucose (1.28 vs. 2.91 mg/dL).
- Over 4 times greater decrease in 2 h pp glucose (-2.28 vs. +7.73 mg/dL).
- A decrease from 6.4 to 5.28 (-1.12) in TG to high density lipoprotein cholesterol (HDL-C) ratio versus an increase (+0.11) in the placebo group.

Based on the positive effects of this RIAA/acacia combination on established clinical markers, researchers concluded that it may be a viable protocol for patients displaying the onset of insulin resistance and metabolic syndrome.<sup>7</sup>

*Study #2: UltraMeal® Plus Medical Food.* A separate 12-week, open-label, randomized, 2-arm clinical trial of 59 postmenopausal women was conducted with UltraMeal Plus (a medical food formula with soy and sterols, but without the RIAA/acacia blend) and its complementary low-GL diet/exercise program versus the American Heart Association’s Step 1 Diet (AHAD) and

exercise. Total caloric intake and exercise were matched in each arm. The medical food arm demonstrated statistically significant decreases in total cholesterol (tChol, 15.8% between-group comparison), low-density lipoprotein cholesterol (LDL-C, 14.8% between-group comparison), and TG (44.8% between-group comparison). In addition, significant improvements were observed in ratios of tChol to HDL-C and of TG to HDL-C, blood pressure, and Framingham CVD risk assessment compared with the AHAD program, which does not consider GL.<sup>18</sup>

**Study #3: UltraMeal® Plus 360° Medical Food.** A 12-week, open-label, randomized, 2-arm clinical trial compared the effectiveness of UltraMeal Plus 360° ingredients (including the RIAA/acacia blend) and the complementary low-GL diet and exercise plan in 44 subjects with metabolic syndrome. Subjects in both arms were placed on the same Mediterranean-style, low-GL diet with no calorie restrictions and a goal of 150 minutes of moderate aerobic exercise per week. Only one arm received the nutritional support of UltraMeal Plus 360° medical food.<sup>19</sup>

Both arms experienced similar weight loss despite having no calorie restrictions. However, the medical food intervention group showed significantly better results in the following key CVD risk factors (Table 1):

- Statistically greater reductions in tChol, TG, tChol/HDL-C ratio, and TG/HDL-C ratio.
- Significant increase in HDL-C.
- Persistent lowering effects on apolipoprotein B (apoB). ApoB is a component of LDL-C and has been shown in studies to be a superior marker in predicting CVD risk because its measure reflects the total number of atherogenic particles associated with narrowing of the arteries via plaque buildup.<sup>20-22</sup>
- Persistent lowering effects on apoB/apoA1 ratio, a newly recognized, important indicator of CVD risk. Apolipoprotein A1 (apoA1) is the main component of HDL-C. This ratio therefore provides an accurate picture of the balance of good and bad cholesterol in the blood; the lower the ratio, the lower the risk.<sup>20-22</sup>
- Greater reduction in the Framingham 10-year CVD risk score.

## CAUTIONS

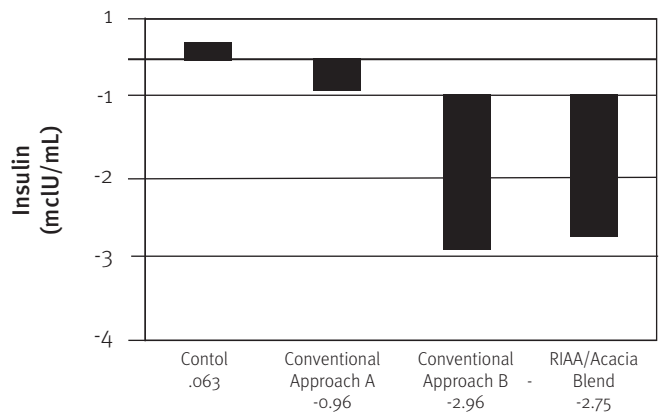
### General

Dietary plans that provide less than 800 calories a day are not recommended. Individuals with a hypersensitivity to ingredients in UltraMeal Plus 360° should avoid use. Individuals with soy hypersensitivities may wish to try UltraMeal® Plus 360° RICE Medical Food.

### Soy and Thyroid Function

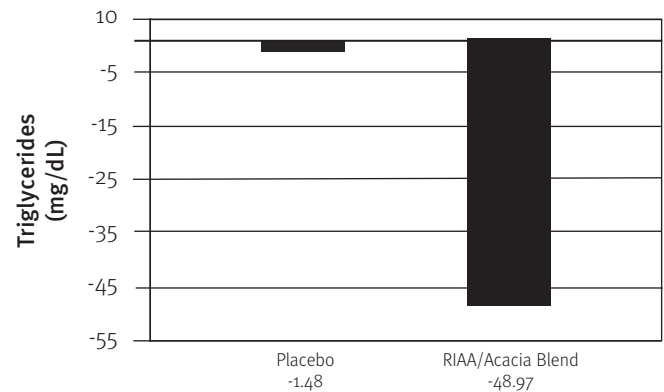
Some individuals who have an underactive thyroid or who may be predisposed to thyroid problems may want to limit their intake of soy. Although the mechanisms are unclear, an effect on thyroid peroxidase has been demonstrated in animal studies. Individuals who are taking thyroid medication may want to refrain from simultaneous ingestion of soy products, as soy may limit the absorption of the medication.

## Significant Insulin Modulation in Animals



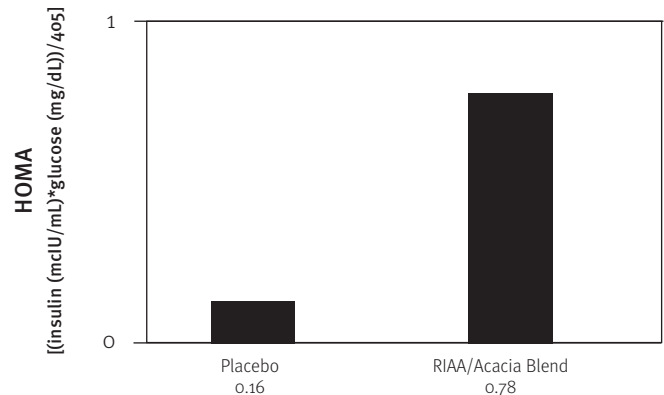
**Figure 1.** In a diabetic mouse model, the RIAA/acacia blend was comparable to leading conventional approaches.<sup>7</sup>

## Improvement in Triglycerides in Humans



**Figure 2.** In an 8-week, double-blind, placebo-controlled study of 91 patients, the RIAA/acacia blend demonstrated a greater decrease in triglycerides.<sup>7</sup>

## Improvement in Insulin Sensitivity in Humans



**Figure 3.** In the same clinical study, the RIAA/acacia blend demonstrated a greater improvement in the homeostasis model assessment (HOMA) in subjects with initial fasting insulin  $\geq$  15 mIU/mL. HOMA estimates steady state  $\beta$ -cell function and insulin sensitivity.<sup>7</sup>

UltraMeal® Plus 360° RICE Medical Food offers a rice-based alternative with RIAA/acacia for those who may be sensitive to soy.

### Pregnancy and Nursing

Due to lack of testing in these individuals, UltraMeal Plus 360° is not recommended for pregnant or nursing women.

### Children

The nutritional content of UltraMeal Plus 360° is based on adult reference daily intakes (RDIs), and no testing in children has

**UltraMeal Plus 360° Program vs. Low-GL Diet Plan & Exercise**  
Summary of Lab Value Changes

Measurement	Arm 1: UltraMeal Plus 360° ingredients with Mediterranean-style Low-GL Diet Plan & Exercise	% Change	Arm 2: Mediterranean-style Low-GL Diet Plan & Exercise Only	% Change
Total Cholesterol (mg/dL)	-36.74*	-14.5%	-16.33*	-6.3%
Triglycerides (mg/dL)	-89.39*	-35.2%	-30.89	-14.3%
HDL-C (mg/dL)	+2.65*	+7.0%	+1.06	+2.7%
LDL-C (mg/dL)	-28.38*	-17.3%	-15.06*	-8.4%
TChol/HDL-C	-1.35*	-19.5%	-0.61*	-8.9%
TG/HDL-C	-3.01*	-42.7%	-1.01	-17.6%
ApoA1	-4.00	-2.1%	-8.44	-4.3%
ApoB	-25.70*	-17.5%	-15.06*	-9.9%
ApoB/ApoA1	-0.12*	-15.4%	-0.05*	-6.3%

**Table 1.** The medical food arm showed significantly greater improvements in CVD risk indicators, including apoB and apoB/apoA1.<sup>19</sup>

been done thus far. For these reasons, UltraMeal Plus 360° is not recommended for use in infants or children under the age of 12.

**ADVERSE REACTIONS**

No serious adverse events reported as of April 2009.

**POTENTIAL DRUG/NUTRIENT INTERACTIONS**

**Anti-Coagulants (Warfarin, Heparin)**

This product is not recommended for individuals taking anticoagulants. UltraMeal® Plus Medical Food (without SKRMs) may be an alternative for those on anticoagulant medications.

**WARNINGS**

**Vitamin A**

Excess vitamin A may be toxic and may increase the risk of birth defects. Pregnant women and women who may become pregnant should not exceed 5,000 IU of preformed vitamin A (retinyl acetate or palmitate) per day.

**STORAGE:** Keep tightly closed in a cool, dry place.

**DOSAGE AND ADMINISTRATION:** Blend (no longer than 15 seconds), shake, or briskly stir 2 level scoops (51 grams) of UltraMeal Plus 360° into 8 fluid ounces of chilled water twice daily, or as recommended. **Consume within 10 minutes of reconstitution.**

**HOW SUPPLIED:**

- 25.5 oz. (714 g) Powder Container (Natural Vanilla flavor) (14 servings)
- 26 oz. (728 g) Powder Container (Dutch Chocolate flavor) (14 servings)
- 25 oz. (700 g) Powder Container (Strawberry Supreme flavor) (14 servings)
- 10 packet (520 g) Box (Variety Pack—3 flavors) (10 servings)

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<sup>†</sup> Saturated fat is contributed by olive oil, which has recognized health benefits.  
<sup>\*\*</sup> Non-genetically engineered, identity-preserved soy protein.  
<sup>\*\*\*</sup> As Metafolin®.  
<sup>\*</sup> Conducted at MetaProteomics, Inc., the nutrigenomic research arm of Metagenics, Inc.  
<sup>\*\*</sup> Conducted at the Functional Medicine Research Center<sup>SM</sup>, the clinical research arm of Metagenics, Inc.  
<sup>\*\*\*</sup> This product is manufactured in a facility that produces products containing soy, dairy, nuts, tree nuts, fish, and shellfish.



Metagenics is committed to using only environmentally-friendly papers and inks.

